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1. Drabkin, D. L.: Metabolism of Hemin Chromoproteins, Physiol. Rev. *31*:345 (1951).
2. The Biosynthesis of Hemoglobin, Editorials, J.A.M.A. *150*:1223 (Nov. 22) 1952.

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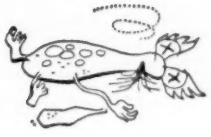

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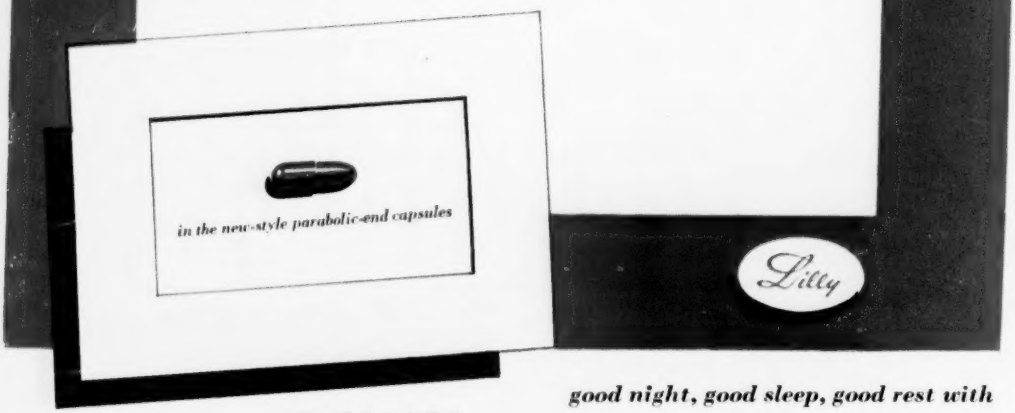

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THE BALANCED CURRICULUM*

SIR HENRY COHEN, M.D., D.Sc., LL.D., F.R.C.P.†

LIVERPOOL, ENGLAND

NO ONE will dispute the importance of the topic assigned to me in this symposium, nor can it be doubted that the core of the problem of medical education lies in the *balanced* curriculum. This is a balance between the pursuit of knowledge for its own sake, for its intrinsic interest and its educational value, on the one hand, and on the other, its pursuit for vocational and technical needs, though the boundaries between are blurred, and most vocational needs can be presented in a liberal context. It is also a balance between the humanities and science since both are essential to the pursuit of culture; between the claims of society and of the individual; between cure and prevention; between the physical and the mental; between different subjects competing for time and place; between teaching and learning, the didactic and the heuristic; between the practical and the theoretical; between providing the rigid necessities of a general curriculum fulfilling a specific aim and satisfying the flexible needs of the individual student; between the economic burden of medical education in terms of time and money, and the service it yields to the community — if the course is too prolonged, the length of service is too short, and if the course is too short the quality of service may suffer. Thus there must be a balance between the *aim* and the *duration* of the undergraduate curriculum. Seventeen centuries ago Galen estimated that since a physician must be a philosopher and possess all the necessary knowledge of life and its manifestations a period of study of at least eleven years was needed to attain this aim. Thessalus on the other hand, who took a poor view of systematic academic instruction, declared that six months only was necessary to make an excellent physician.

These facets of the problem of the balanced curriculum, chosen at random, justify placing my contribution at the end of this section's deliberations, for in large measure it must recapitulate — summarizing, criticizing and endeavoring to synthesize views expressed during this conference, and reemphasizing the conclusions of the British Medical Association Committee on the Training of the Doctor. I am both pleased and gratified to find that the form of this committee's report gives the pattern to the program of this conference, and that the views it expressed have received such support and approbation this week. If much that I have to say is by way of reiteration I find comfort in the reflection of the French author who observed, "Everything has been said before, but since nobody seems to listen we have to say it all over again."

Diagnosis must precede rational treatment, so I propose to discuss several major defects of the curriculum that have contributed to its lack of balance, and to suggest in general terms how, by recognizing the faults, one may overcome them. These vary in importance but all are, I hope to show, both significant and relevant. Their correction must ignore personalities, traditions and purely departmental interests in the endeavor to provide a smooth, continuous, poised program in which co-ordination, integration and collation — the semantic trinity both blessed and beloved by the planner — will be achieved.

It is beyond the theme of my contribution to discuss in detail the "balanced" aspirant to a medical training. I shall assume that the raw material coming to us from the schools has the basic qualities — a good general education, intelligence, industry, zest, general aptitude, probity, personality and character; that some will possess the manual skills and dexterity necessary for surgery; that others will have an abundance of that tact, human sympathy and equanimity necessary for the family doctor and the physician; and that yet others will show greater interest in the more scientific technics of pathology or radiology, for example, but that all are destined to play a role in the drama of the relief of human suffering.

The first criticism I would level is that our overcrowded and confused curricula are inevitable while we vacillate between whether the aim of the undergraduate curriculum is to produce a good general practitioner or to lay the foundations of a medical career whatever branch of medicine is later to be followed. Unless we know where our goal lies we cannot prepare resolutely the path that leads to it. In Great Britain and Ireland we are in a measure

*An address delivered at the First World Conference on Medical Education, London, England, August 28, 1953.

†Professor of medicine, University of Liverpool, England

fettered in the shackles of a restrictive legislation. The law provides that for registration as a legally qualified practitioner candidates shall show a standard of efficiency at their final examination that shall "be such as sufficiently to guarantee the possession of the knowledge and skill requisite for the efficient practice of medicine, surgery and midwifery." For more than sixty years this legal requirement remained unaltered though we have now made the intern year compulsory.

Yet the field of medical knowledge has expanded with almost unrestrained acceleration. Spectacular discoveries in diagnosis and treatment have made increasing specialism in their technics inevitable, so that today there are at least thirty recognized special branches of medicine, to any of which a doctor may confine his interests. Notable advances in medicine have changed the natural history of disease. Meningitis, pneumonia, malaria, bacterial endocarditis and diphtheria, to mention only a few infections, must be portrayed today in patterns that were unknown twenty years ago. The use of special procedures has enabled us to explore by x-rays practically every crevice and cavity of the body. Improvements in technic and measures for controlling infection, hemorrhage and shock, have made practicable and safe the surgery of the brain, the heart and the lungs in a manner undreamt of even a generation ago. The lowering of infantile mortality and the achievements of preventive medicine have so prolonged life that added importance attaches to the chronic diseases of later life and the care of the aged. The influence of mental factors in physical disease and the social and industrial implications of disease are emerging from a too prolonged neglect. And practically no advance in physics or chemistry is without its influence on medical research and practice. Even in the last decade developments in enzyme chemistry, immunology, chemotherapy, electron physics and radiophysics promise to solve many fundamental physiologic and biochemical problems, and to add to the therapeutic armamentarium. And the expansion of the social sciences reflected in medical economics increases our responsibilities and fields of action.

With so vast an increase in the corpus of medical knowledge it may well be asked how the doctor can any longer be expected on qualifying to "possess the knowledge and skill requisite to the efficient practice of medicine, surgery and midwifery" — that is, to be an efficient general practitioner. The answer is compelled by the inexorable pressure of expanding knowledge.

The undergraduate curriculum cannot embrace the whole theory and practice of medicine. It cannot provide the detailed systematic knowledge of the basic sciences essential to many special branches of medicine. Nor can it present in detail all the ills to which mankind is heir, nor consider all the agents of nature and nurture, of the individual and of society, that may affect the human being favorably or unfavorably. And above all it cannot attempt to teach the technics required in the practice of specialties. It must limit its aim to laying the foundations of the doctor's training; it should be concerned not with presenting masses of factual data, but with indicating the scope, potentialities, duties and responsibilities of medicine, both curative and preventive; it must emphasize with cogent illustration the basic principles that are indispensable to all forms of medical practice. In exploring the world of medicine the student should be guided in methods of map reading, but his knowledge of detail should lean to the three-miles-to-the-inch scale, rather than one-mile-to-three-inches. There must be left to postgraduate study and training the preparation of the doctor for his special vocation in medicine. Above all, since medical knowledge is ever expanding, the undergraduate curriculum must favor the acquisition of enduring habits of work and thought and of enthusiasm for study, so that the doctor shall remain a student throughout his professional life. The growth of knowledge in both medicine and in educational methods means that "a curriculum can never be final; it is always moving to that end, but it never arrives."

Here surely is an opportunity for experiment in countries whose legislation permits. Could not there be built in four years, on the foundations of a good general school education, a medical course that would serve as an introduction to any branch of medicine, followed for the family doctor by two or three years' training for general practice, which would vary with the special needs and available resources of the country and cover the diagnosis, prevention and treatment of the diseases commonly encountered there? And for other specialties a postgraduate training dependent on their individual requirements? I believe that it could.

The second defect arises only in part from the first. The student must be made aware of the contribution to medicine of new branches of knowledge, of technical developments and of changing emphasis. But how have we hitherto dealt with these? We have accommodated them by a process of "accretion," and the birth of new disciplines such as social medicine, the newer psychiatry, radiology, statistics and the history of medicine. Isolated snippets of allegedly "useful" information have been added to an already overcrowded syllabus so that too often it merits the phrase that Cromwell used of the laws of England — "a tortuous and ungodly jumble." Now it may well be that in many of these subjects a brief introductory special course is necessary, but as far as possible the new should be incorporated by a pruning, reorganization and reorientation of the existing subjects of the curriculum. And here I would emphasize the basic pedagogic principle that we should seek to apply throughout the curriculum: that we

soon forget what we have learned if we do not constantly use and review it, and relate it to other knowledge. Let us particularize. With mathematics fresh in his mind the student should be given a few lectures on statistics early in his course. But then throughout the course all teachers should apply the lessons to be learnt — the range of normal in, say, human heights and weights at given ages, in blood pressure and the size of red cells, the clinical evaluation of drugs, the significance of operative mortality and the like. And so with history — a few introductory lectures on the peaks but then each teacher should interpret his subject in the light of its historical evolution. As one example, every student in his physiology course should be made to read Harvey's *De Motu Cordis;* in it he will find not only history but also the perfect exemplification of scientific method. The selection of the cold-blooded animal and its slowly beating heart as most appropriate for the more precise analysis of the sequence of auricular, ventricular and arterial systole; experiments on the veins designed to validate the hypothesis of circular motion; the inescapable inference that capillaries exist even though not visible by any of the then available means; and the curious lapse that led Harvey to neglect the crucial experiment, the final proof by perfusion of the continuity of artery and vein, though he knew of this method. And one should recall, whenever it is relevant, the light thrown by nomenclature on the evolution of understanding of disease — why "rheumatism" with its origins in a humoral pathology remains a vague concept; why "ataxia" is a descriptive and not an anatomic name; why pituitary gland and pituitous catarrh are related names. And so with social and preventive medicine. There is ample opportunity to illustrate their significance in all branches of clinical medicine so that they become an integral and inescapable part of medicine, not autonomous, independent and unrelated disciplines. In the interests of the students we must resist the pressure of heads of departments urging the claims of their special subjects whether these arise from a sincere belief in their importance, a mistaken sense of prestige, or the financial implications in schools where the size of a departmental grant, and the remuneration of its staff, are proportionate to the number of student hours spent in the department.

The third disrupting factor in the undergraduate curriculum stems from the increasing specialization both in the basic medical sciences and in the practice of medicine. This reveals itself in several ways. On the clinical side the teacher, to keep abreast of instrumental methods in diagnosis and to acquire the necessary skill in craftsmanship, limits his field of experience in medicine or surgery; secondly, and consequentially, the clinical material in his beds follows a narrow pattern — thyroid glands or prostates, cardiac disease or colitis. In the field of basic science the teacher tends to present his subject as an autonomous, isolated compartment of knowledge unrelated to the main stream or purpose of medical education. Thus, fragmentation of instruction results — a patchwork quilt, not a continuous design woven into the fabric. And whether we teach by subjects or systems, by blocks, vertical or horizontal, the outcome is the same — a conception of man as a particulate, as an atomized being. An examination of most curricula will reveal too great isolation not only of different departments but also of various stages of the curriculum. Indeed, this is illustrated by the terms we use for the different stages — *pre*-medical, *pre*-clinical and clinical — as if each were simply an introduction to the other instead of the curriculum's being a continuum in which the knowledge and methods of science lead through a study of the normal, in all its phases and relations, to a study of disease in the "whole" man. This "holistic" outlook, to use Smuts' phrase, this synoptic view, reflects the truism that man is greater than the sum of his parts. Unless the synoptic purpose of medical training is achieved the curriculum will be misdirected in aim, in structure and in balance.

But the synoptic view is not simply of man as an individual, "extracted from his realm" and treated as "a thing apart." It sees man also as a member of a family and as a unit in society. In the days when apprenticeship formed part of the medical student's training, many of the social aspects of medicine could be culled from daily experiences in the patient's home. Today we must still provide for this experience in our undergraduate curriculum — not better to prepare the undergraduate for general practice but to give him a balanced view of medicine as a single discipline. Most clinical training will be carried out in hospital and polyclinic, but the student must ever have it borne in on him that when a patient comes into the hospital he leaves his environment, his occupation, his family and his friends behind. Yet these might well have played a major part in the genesis and course of his illness. The patient in the hospital — clean, well clad, tidy, lying in a comfortable bed and eating three good meals a day — is often a very different being in the squalor, anxieties and discords of his home and job. The student today sees too little of the conditions in which disease thrives — the overcrowded, ill ventilated and unheated homes, the undernutrition that results from poverty, the effects of chronic illness in the home, the moral cankers of unemployment and the like. A balanced training must ensure that the doctor is not a man of confined vision.

There is another feature of the unbalanced curriculum that is closely related to its "holistic" needs. It is perhaps not surprising that the tremendous victories of science in the conquest of disease, especially in the past few decades, should have led to a neglect

of the more personal aspects of a doctor's work. Yet the balanced curriculum will include the lessons that the humanities hold for medicine. It is premature to equate the practice of medicine with clinical science. The fields of medicine in which the technics of science are applicable, are limited, and, unlike science, medicine cannot always wait for an answer. It may have to act on incomplete data and to choose between equally sustainable provisional diagnoses. Here the student must learn that science must yield to pragmatism. Nor can medicine concur in Lord Kelvin's reported dictum that "only when natural phenomena can be measured are they to be clearly apprehended." Many medical problems defy measurement, for human life has many imponderables. We cannot yet regard man simply as a physicochemical mechanism. He has emotions and appetites that cannot yet be measured, though they influence his welfare profoundly. His loves and hates, his passions and fears, his worries and anxieties, his daily stresses and strains, all may express themselves in bodily disturbances. The thumping heart, the cold sweat, the weak and tremulous knees of fear are but simple evidences of this untenable dichotomy of body and mind. And just as we may lead a horse to water but fail to persuade it to drink, so the scientist who is not also a humanist will possess his instruments and therapeutic weapons in vain, if he cannot persuade a patient to their use. The health problems of Jack Smith, and of the family and the society in which he lives, are the concern of a medical training designed to make every doctor in a sense both a natural philosopher and a humanist.

If this is to be achieved two points should be made about the teachers. Too often our teaching staffs are recruited from those whose claims to academic posts are based on original contributions to knowledge. No one contests that universities and medical schools exist both to transmit and to extend knowledge, but these demand different qualities not always found in the same person. The teaching staff will do better work under the stimulus of research, but there must be a proper balance between research and teaching and teachers must have the necessary experience and capacity to teach. Teaching is an art and, especially in medicine, in which the approach to the patient is of such importance, precept without worthy example is apt to be sterile. Again, a noteworthy lack of co-ordination is revealed at different stages of the curriculum because of a failure of the clinical teacher to keep abreast of the nomenclature and concepts of the basic medical sciences. Two examples are sufficient: although it is now thirty years since anatomists adopted their present nomenclature many clinicians cling to the old to the confusion of their students, and this by a vicious circle perpetuates itself, for the student entering the wards so familiarizes himself with his teacher's terms that when he too becomes a teacher he uses them; and so it is with therapeutic agents condemned by teachers of pharmacology and therapeutics on the basis of controlled clinical trials, but approved and applauded by the clinician on the flimsy foundation of clinical impression. Teachers must themselves keep abreast of developments in basic subjects if poise is to be achieved and the conflicts and contradictions so damaging to the immature but developing mind are to be avoided.

I now turn to what I believe to be a major factor in the lack of continuity and the imbalance of the curriculum. It lies in the concept of disease. For too long our teaching and our textbooks have been dominated by the concept of disease enunciated by Sydenham. Diseases are regarded as "entities" with a natural history and pathognomonic signs that distinguish one from the other; in their description little or no regard is had for the underlying mechanisms, and so the real business of medicine is thought to begin in the wards, and the basic disciplines of anatomy, physiology and psychology regarded as tedious and largely profitless — as obstacles to be surmounted before useful medical studies can be started. Now although the use of the term, "a disease," is in the Sydenham sense a convenient conceptual symbol, as the basis of medical training it is misleading and irrational. Disease must be regarded simply as a deviation from the normal; hence the need to know the normal and the variations that fall within the normal range. Many of the terms we use indicate these quantitative deviations from the normal: constipation and diarrhea; polycythemia and anemia; hypertension and hypotension. But many of these deviations recur in uniform patterns. They then indicate one of four groups of change: first, *anatomic*, — for example, a bitemporal hemianopia indicating an interruption of the optic chiasma; secondly, *physiologic*, such as wasting, thirst, polyuria and glycosuria, indicating not a disease, diabetes mellitus, but an impairment of carbohydrate metabolism; thirdly, *pathologic* — for example, redness, swelling, heat and pain, indicating inflammation (not confined to infection); and finally, *etiologic* factors, such as physical, psychologic, social and occupational, each suggested by the patient's history and signs. A complete diagnosis will cover all four groups. It is impossible here to develop this theme fully, but I hope I have said enough to indicate that on this foundation we recognize diseases not by their special signs, as we would the species of a plant or animal, but in terms of disturbances of anatomy, physiology, psychology and sociology, interpreted in the light of pathology; thirty years' experience of teaching has convinced me that this is an infinitely firmer groundwork from which to develop a co-ordinated, rational, smooth and balanced preparation for the study of medicine than that based on describing "diseases," and that it corrects a major manifestation of imbalance in the curriculum.

We have all protested against the student's being called upon to assimilate a vast mass of unrelated facts, which increase in number with the expansion of knowledge, and we seek too often the least painful means of spoon-feeding these facts to him. Man cannot think without facts, but he cannot think with facts alone. If he is to retain them they must be allied to principles and to earlier acquired knowledge, and those he needs to memorize should be kept to a minimum. He should, however, be instructed where he can find such information as he may need, and how to use a library. The practice of medicine often demands urgent action; it is the knowledge of this that must be acquired and immediately available. The good teacher will constantly try and generalize — for example, the principle that the intensity of symptoms is directly proportional to the rate of development of the pathologic change responsible for them covers a vast number of facts from pneumothorax to intracranial tumor. Teachers should not be afraid of these generalizations; they may have to be modified with advancing knowledge, but their begetters may take comfort from the reflection that so too had Newtonian gravitation in the light of relativity.

Finally, I believe that the balanced curriculum must provide enough free time for leisure and reflection, and be sufficiently elastic to allow for the varying needs of individual students who may show special abilities.

There is, as I hope I have hinted, a need for experiment in curricula; today in almost every country they are too rigid; all show similar patterns of traditional origin. But in designing any such experiment for a balanced curriculum I suggest that it should aim at ensuring that at the conclusion of his undergraduate career the student fulfil the following desiderata:

Firstly, he shall have acquired the basic medical knowledge and technics that will prepare him not simply for general practice but also for any specialty so that he retains a general outlook and appreciates the significance of advances in general knowledge for his chosen branch of practice.

Secondly, he shall have developed habits of logical thought and critical judgment of evidence and experience that will prevent his falling a victim to indefensible faiths and seductive fallacies. For him "post hoc" will not be a sufficient therapeutic criterion; correlations will not always be causal; nor will he to "the fascination of a name, surrender judgement, hoodwinked."

Thirdly, he will know where and how to seek help and acquire knowledge both from men and from books. "You cannot learn men from books," said Disraeli; but to study medicine without books is, as Osler wrote, "to sail an uncharted sea."

Fourthly, he will have the urge to continue self-education in the wise and critical spirit of Plato's dictum that "Education is a lifelong business."

Fifthly, he will have acquired a rational approach to medicine and recognized that there are uses as well as limitations to empiricism, that patients are living sentient beings and not simply "cases" and that, in the words of Trousseau, "There are no diseases, only sick people."

Sixthly, he will have been made more fully aware of his obligations and responsibilities as a doctor to the individual and to the community, and will shape his conduct by the ethical and moral principles of his profession.

Seventhly, and lastly, he shall be a cultured and educated gentleman, seeking wisdom through knowledge, cultivating and cherishing his ideals, ready to meet a challenge and grasp an opportunity for service to his fellow men, remembering that he can cure and prevent only occasionally, relieve often but comfort always.

I do not claim to have made a novel contribution to this conference, but there have, I hope, emerged from this analysis of the causes of imbalance in our present-day curricula, defects so challenging that action is not only desirable but compelling. It is for those here to initiate such action, and so to ensure that the deliberations of this conference will bear fruit and not be dismissed, and its transactions pigeonholed, as mere intellectual exercises. For we who are teachers must never forget that we have been entrusted with a task whose place in the scheme of things Cicero implied when he asserted that "Men never come closer to the gods than in giving health to men."

THE VALUE OF A SINGLE INJECTION OF THYROTROPIN IN THE DIAGNOSIS OF OBSCURE HYPOTHYROIDISM*

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ALTHOUGH full-blown myxedema is readily diagnosed, there are many persons in whom a question of hypothyroidism arises, but the clinical picture and customary tests of thyroid function are not sufficiently characteristic to establish a diagnosis. This is particularly true of patients who have been taking thyroid, for in them not only are laboratory tests obscured by the effects of the medication, but also withdrawal of the drug may be followed by a period of hypoactivity of the gland even though function may have been normal before therapy. The establishment of a diagnosis in such cases may require a prolonged period of observation, which can be trying to the patience of both the physician and the patient. A test that would enable immediate determination of potential thyroid function, whether or not thyroid was being taken, would therefore be of considerable help to the clinician.

Several investigators[1-5] have reported the use of thyrotropic hormone (TSH) to differentiate primary hypothyroidism from hypothyroidism secondary to pituitary insufficiency, injecting one or more doses daily for several days and following changes in basal metabolic rate, serum cholesterol, serum protein-bound iodine, and twenty-four-hour or forty-eight-hour uptake of tracer doses of radioactive iodine. In 1949 Stanley and Astwood[6] demonstrated that a single injection of TSH increased the rate at which the normal human thyroid gland takes up administered radioactive iodine. They also noted that an increased rate of uptake occurred even while the patient was receiving thyroid. This effect of TSH was found to begin approximately eight hours after its injection, to be maximal on the second day and to disappear after three or four days. The authors made these studies by repeated measurements at intervals of thirty to sixty minutes and determination of the rate of uptake by plotting the slope of the Geiger counts against the square root of time.

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These findings suggested that it might be possible to devise a simpler, shorter method of determining the ability of the thyroid gland to respond to stimulation in persons either on or off thyroid medication. Such a test should be of value not only in rapidly establishing a diagnosis in obscure cases of hypothyroidism but also in the study of thyroid function in various conditions.

METHOD AND MATERIAL

Since it was desirable to keep the test as simple as possible and to have it suitable for outpatients as well as hospitalized persons, it was decided to study the effect of a single injection of TSH upon the thyroid uptake of I^{131} (radioactive iodine) over a three-hour period on two successive days, the uptake of the first tracer indicating the control rate and that of the second the response to TSH. The schedule of the test was as follows. On the first day, at 9 a.m., a tracer dose of I^{131} without added carrier was given orally with the subject in a fasting state to facilitate absorption. Three hours later the uptake was measured with the counter positioned over the thyroid gland, correction being made for background activity as determined by counts made over the lower thigh. Immediately after this, a single injection of TSH, in a freshly prepared saline solution, was administered intramuscularly. On the next day, twenty-four hours after the administration of the first tracer, residual thyroid radioactivity was counted, and a second tracer, containing the same dose of radioactivity as the first, was given orally in the fasting state. Three hours later, measurement of the thyroid uptake was again performed. The effect of TSH was evaluated by the difference between the three-hour uptakes of the tracer doses given before and after administration of the hormone. In some cases samples of blood for protein-bound iodine determinations (PBI) were drawn just before and twenty-four hours after the injection of TSH.

In earlier tests on adults, tracers of 25 microcuries were used, but later, after the acquisition of a more sensitive scintillation counter, doses of 10 microcuries were employed. In children under ten years of age, smaller tracers of 3 microcuries were administered, and between the ages of ten and seventeen years, 5 microcuries were given.

Two relatively pure preparations of TSH in the form of lyophilized powder** were used in this study.

**The preparations of TSH used in this study were generously supplied by the Armour Laboratories. They were not absolutely pure, insignificant amounts of certain other pituitary principles being present.

Lot J 13903-R was employed in the first 15 tests performed, and K 46808-R in all subsequent tests. No apparent difference in thyroid responses to similar doses of the two preparations was noted. Initially a 20-mg.* dose was used, but after it was found that 10 mg. produced an adequate response, the smaller dose was subsequently employed.

Serum PBI was assayed by a modification of the method of Barker,[7] each sample being run in duplicate. From a careful evaluation of a series of 58 determinations in duplicate it seems reasonable to consider a change of 1.0 microgm. per 100 cc. or greater between levels before and after TSH to be significant.

Several groups of subjects were tested: normal adult volunteers, whose tests served as controls; patients with known primary hypothyroidism; a patient with pituitary insufficiency; and patients in whom for various reasons the question of the presence of hypothyroidism had been raised. The last group included patients with symptoms suggestive of hypothyroidism in whom the usual laboratory tests were equivocal, and patients with ovarian dysfunction, habitual abortion and oligospermia who were considered possibly hypothyroid. Some of these patients were receiving thyroid at the time of the test, but those who had recently been given iodine-containing x-ray mediums were excluded since these substances are known to interfere with both the uptake of I^{131} and the determination of serum PBI.

Results

To demonstrate that the technic of the test, except for the administration of TSH, would cause no change in I^{131} uptake on the second day, 2 normal persons were given the tracer doses and their thyroid uptakes counted according to the schedule of the test, but administration of TSH was omitted. In each case the two successive I^{131} uptakes showed no significant differences, measuring 5.0 to 5.7 per cent in 1, and 7.9 and 7.6 per cent in the other.

*Dosages are expressed as milligram equivalents to Armour Standard 2R3; 2.5 mg. of this standard is equivalent to 1 *USP* unit of TSH.

These findings are consistent with those of Stanley and Astwood,[6] who noted no significant difference in the I^{131} uptake rates determined on the same persons on successive days.

Response of Normal Subjects

Eight normal persons between the ages of twenty and fifty, 4 male and 4 female, were tested with doses of TSH varying from 4 to 20 mg. (Table 1 and Fig. 1). All showed a considerable increase in uptake on the second day as compared with the first, the mean difference being 11.1 ± 3.8 per cent, and the response after 4 mg. was as great as that seen with 20 mg. Since 10 mg. was a conservative dose, easily handled and producing few, if any, side effects, it was established as the standard dose

TABLE 1. *Effect of a Single Injection of TSH on the Three-Hour Uptake of I^{131} in Normal Subjects.*

Test No.	Sex	Age	Dosage of TSH	Three-Hr. Uptake of I^{131}†		
				Before TSH	After TSH	Change
		yr.	mg.*	%	%	%
3	F	22	20	15.9	33.5	+17.6
5	F	46	20	12.4	25.2	+12.8
25	M	46	10	6.8	13.9	+ 7.1
30	M	22	7	8.7	20.5	+11.8
33	F	37	4	17.8	33.3	+15.5
35	F	36	10	4.4	12.7	+ 8.3
40	M	50	9	7.8	14.7	+ 6.9
43	M	20	10	11.5	20.5	+ 9.0
Mean				10.7	21.8	11.1
S.D.				± 4.5	± 8.2	± 3.8

*In this and in subsequent tables dosage is expressed as milligram equivalents of Armour Standard 2R3.

†In this and in subsequent tables uptake is expressed as percentage of the tracer dose measured over the thyroid gland, corrected for background and residual radioactivity.

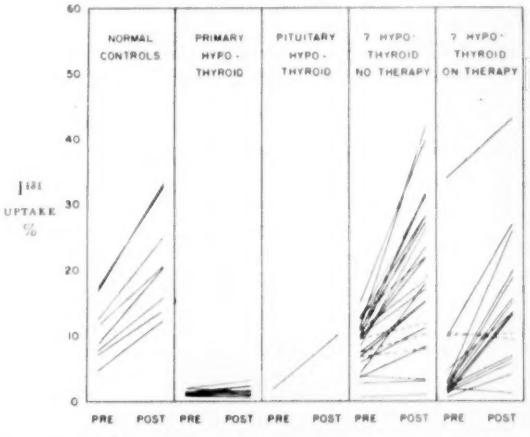

FIGURE 1. *Effect of a Single Injection of TSH on the Three-Hour Thyroidal Uptake of I^{131} in Various Conditions.*

In this and in subsequent figures the uptake is plotted as percentage of the tracer dose measured over the thyroid gland, corrected for background and residual radioactivity. The levels before and after TSH are connected with a line, the slope of which reflects the degree of response. The broken lines in the two columns on the right indicate tests suggesting low thyroid reserve.

for most of the subsequent tests. It is interesting to note that Perlmutter et al.[8] reported similar findings in their studies, utilizing the twenty-four-hour uptake of I^{131} and changes in the serum protein-bound iodine determined at twenty-four-hour intervals, to determine the minimal effective dose of TSH in human beings.

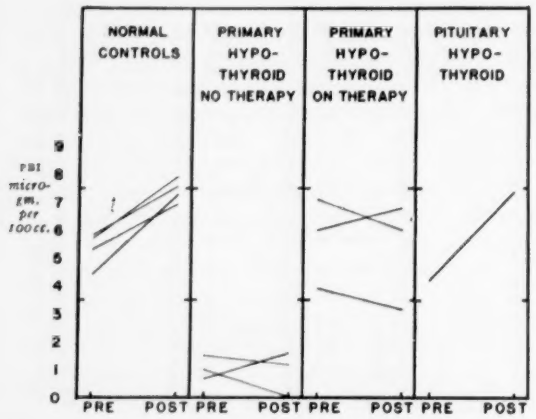

FIGURE 2. *Effect of a Single Injection of TSH on the Serum Protein-Bound Iodine (PBI) in Various Conditions.*

The normal range of serum PBI, 3.5 to 7.5 microgm. per 100 cc., is indicated on the scale. The levels before and after TSH are connected with a line, the slope of which reflects the degree of response. The test on the patient with hypothyroidism secondary to pituitary deficiency was performed during the administration of 0.016 gm. of thyroid daily.

The responses of the serum protein-bound iodine of 4 normal persons to single injections of 10 mg. of TSH are shown in Figure 2 and Table 2. It may be seen that a significant rise occurred in each case, consistent with an increased output of thyroid hormone.

Primary Hypothyroidism

Tests were performed on 7 patients in whom the diagnosis of primary hypothyroidism had already been established by characteristic clinical and laboratory findings (Fig. 1). Their ages varied from thirty-three to sixty-four years, and there were 2 males and 5 females. It is evident not only that the initial uptakes of this group were much lower than those of the normal subjects, but also that TSH had no appreciable effect in any case, the mean uptake being 1.45 ± 0.36 per cent before and 1.45 ± 0.86 per cent after TSH.

Since all but 1 of these patients with primary hypothyroidism were receiving thyroid medication at the time of the test, the question of whether the medication in any way inhibited the response to TSH arose. Although others had demonstrated that the ingestion of thyroid did not prevent a response to single[6, 8] or multiple[4, 5] injections of TSH, the difference in technic used in this study necessitated a determination of the effect of prolonged thyroid administration on the response to this test.

Effect of Thyroid Medication

Three patients who had been receiving thyroid medication for between three and twenty-four months, and who were subsequently found not to have hypothyroidism, were tested while still receiving thyroid and again at intervals of five to eight weeks after its withdrawal (Table 3 and Fig. 3). It is evident that, although thyroid medication inhibited initial uptake, the response to TSH was definite and brisk. Hence, the lack of response seen in cases of primary hypothyroidism could not be attributed to the ingestion of thyroid.

The PBI determinations of 3 hypothyroid patients receiving no medication revealed a low initial level with no significant increase after TSH, and 3 hypothyroid patients on treatment with thyroid had a normal initial level with no appreciable increase after TSH (Table 4 and Fig. 2).

TABLE 2. *Effect of a Single Injection of TSH on the Serum Protein-Bound Iodine (PBI) in Normal Persons.*

Test No.	Sex	Age	Dosage of TSH	Serum PBI		
				control	24-hr. after TSH	change
		yr.	mg.	microgm./100 cc.	microgm./100 cc.	microgm./100 cc.
43	M	20	10	5.7	7.9	+2.2
68	F	45	10	4.4	7.2	+2.8
76	F	51	10	5.8	7.6	+1.8
78	F	41	10	5.3	6.9	+1.6
Mean				5.3	7.4	+2.1

Hypothyroidism Secondary to Pituitary Insufficiency

A patient with panhypopituitarism was tested (Fig. 1). He was sixty years of age and had experienced symptoms of pituitary insufficiency, including dryness of the skin, sensitivity to cold and constipation, for fifteen years. Thyroid had not been administered before the test. Although the test demonstrated a low initial uptake (1.7 per cent) consistent with subnormal thyroid function, there was a good response to TSH, the uptake increasing to 9.7 per cent, indicating a deficiency of endogenous TSH

stimulation rather than primary disease of the thyroid gland. As one might have expected, this test was similar to those of the normal persons receiving thyroid medication, in whom endogenous insufficiency in this disease.[10] Obviously, additional studies are necessary to clarify this question.

Although serum PBI determinations were not performed with the first test on this patient, a

TABLE 3. *Effect of Ingestion of Thyroid on the Three-Hour Uptake of I^{131} and Its Response to TSH in Normal Subjects.*

SUBJECT	SEX	AGE	THYROID MEDICATION	DOSAGE OF TSH	THREE-HR. UPTAKE OF I^{131}		
					BEFORE TSH	AFTER TSH	CHANGE
		yr.	gm./day	mg.	%	%	%
M. M.	M	38	0.064 (for 3 mo.)	10	4.6	13.5	+ 8.9
			None for 5 wk.	20	8.3	26.3	+18.0
B. B.	F	25	0.128 (for 1 yr.; reduced to 0.064 gm. for 2 wk. before test)	20	2.4	19.7	+17.3
			None for 8 wk.	20	15.1	39.7	+24.6
C. G.	F	20	0.256 (for 2 yr.)	20	1.1	13.2	+12.1
			None for 8 wk.	10	10.6	18.4	+ 7.8

TSH was presumably inhibited by the exogenous thyroid medication. It seems unlikely that the thyroid glands of all patients with hypopituitarism would respond so well, since Sheehan[9] describes cases

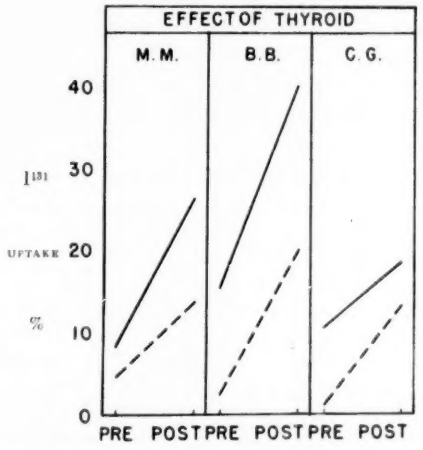

FIGURE 3. *Effect of a Single Injection of TSH on the Response of the Three-Hour Thyroidal Uptake I^{131} in Normal Persons on and off Thyroid Medication.*

Tests performed while the subject was not receiving thyroid are indicated by the solid lines, and those while the subject was receiving thyroid by the broken lines.

of long standing in which the gland had become fibrotic, and Querido and Stanbury[4] describe a case of Sheehan's syndrome of fifteen years' duration that failed to show a significant rise in either the serum level of protein-bound iodine or the basal metabolic rate after nine days of TSH administration. It is possible, however, that, if the thyroid gland is able to respond at all, it may respond to a single injection rather than requiring more prolonged stimulation such as one may see with adrenal

subsequent test carried out while he was receiving 0.016 gm. of thyroid daily revealed a good response in the PBI levels — from 4.2 to 7.4 microgm. per 100 cc. (Fig. 2).

Effect of Iodine Exposure

A graduate nurse tested had a normal control three-hour I^{131} uptake, but her response to TSH was poor (Fig. 4, left column). This test suggested a low thyroid reserve, but since she worked in the operating room, a question of possible effect from

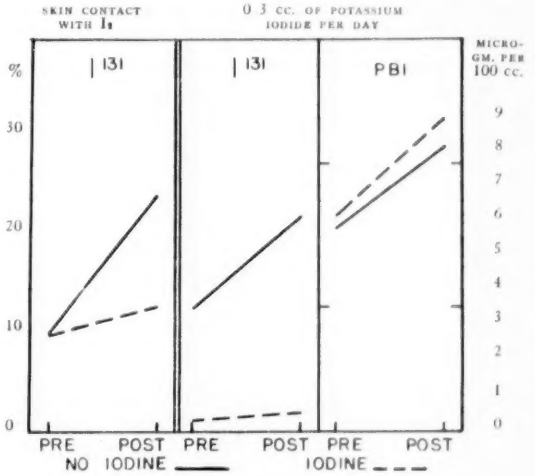

FIGURE 4. *Effect of Iodine on the Response to a Single Injection of TSH.*

Tests performed after administration of iodine are indicated by the broken lines. The column on the left shows the effect of mild exposure to iodine-containing solutions by skin contact, and the other two columns the effect of ingestion of 0.3 cc. of a saturated solution of potassium iodide for a week before the test.

exposure to iodine-containing solutions arose. Accordingly, three months later, on her return from a three weeks' vacation, the test was repeated. This time her response to TSH was normal. Hence, her

exposure to iodine was apparently sufficient to mask the response to TSH, even though it was inadequate to block completely the uptake of the tracer dose of I^{131} by the thyroid gland. Similar results have been seen with patients who have had tincture of iodine painted on the skin or intravenous pyelograms a few days before the test.

To investigate further the effects of I^{127} on the test, a normal volunteer whose TSH response had already been shown to be normal was given 0.3 cc. of a saturated solution of potassium iodide (230 mg. of I_2) daily for seven days. At the end of this period the test was repeated, with determinations of serum PBI as well as I^{131} uptake. The other two columns of Figure 4 illustrate the results. It may be seen that this dose of iodide blocked the uptake of I^{131} both before and after TSH, but a rise in serum PBI occurred. Hence it is evident that although exposure to iodide may invalidate the I^{131} uptake, the response to TSH may be detected by a rise in serum protein-bound iodine.

Examination of the group not receiving thyroid (Fig. 1), demonstrates that the responses fall into three general patterns. The majority (19 tests) showed an increase in I^{131} uptake comparable to that seen in normal controls, the mean uptake before TSH being 9.8 ± 2.7 per cent, as compared with 25.5 ± 6.6 per cent after TSH, with a mean increase of 14.5 ± 6.8 per cent. These tests were consistent with a normal thyroid reserve, and the symptoms could therefore not be attributed to hypothyroidism. Three patients had a low initial three-hour uptake followed by no significant response to TSH, a pattern similar to that seen in primary hypothyroidism. Three (indicated by broken lines) had an initial three-hour uptake within the normal range, but failed to respond appreciably to TSH stimulation, suggesting a low thyroid reserve. The results of the tests showing abnormal responses are presented in Table 5.

TABLE 4. *Effect of a Single Injection of TSH on the Serum Protein-Bound Iodine in Primary Hypothyroidism.*

Test No.	Sex	Age	Thyroid Medication	Serum Protein-Bound Iodine		
				Before TSH	24-hr. after TSH	Change
		yr.	gm./day	microgm./100 cc.	microgm./100 cc.	microgm./100 cc.
41	F	55	None	0.7	1.6	+0.9
71	F	59	None	1.0	0.0	−1.0
77	F	35	None	1.5	1.2	−0.3
46	M	34	0.2	6.0	6.8	+0.8
51	F	60	0.1	3.9	3.2	−0.7
106	F	21	0.12	7.1	6.0	−1.1

TABLE 5. *Abnormal Responses to a Single Injection of TSH in Questionable Hypothyroidism.*

Test No.	Sex	Age	Thyroid Medication	Dosage of TSH	Three-Hr. I^{131} Uptake			Final Diagnosis
					Before TSH	After TSH	Change	
		yr.	gm./day	mg.	%	%	%	
8	F	9	None for 2 mo.	20	0.6	0.9	+0.3	Primary hypothyroidism
71	F	59	None	10	3.7	3.3	−0.4	Postoperative hypothyroidism
77	F	35	None	10	2.6	3.0	+0.4	Hypothyroidism after I^{131} therapy
53	F	46	None	10	7.4	10.1	+2.7	Low thyroid reserve
13*	F	26	None	20	6.6	7.9	+1.3	Low thyroid reserve
76	F	51	None	10	9.4	11.9	+2.5	Probable iodine exposure (see text)
11	F	25	0.065 (for 3 mo.)	20	1.9	1.4	−0.5	Primary hypothyroidism
34	F	19	0.032 (for 4 wk.)	20	9.8	10.2	+0.4	Low thyroid reserve
69*	F	26	0.065 (for 2 mo.)†	20	10.3	9.3	−1.0	Low thyroid reserve
65	F	9	0.1 (for 4½ yr.)	10	33.9	43.2	+9.3	Cretinism, with goiter

*Same patient.

†After the preparation of this manuscript it was found that this patient had stopped her thyroid medication a month before this test.

Suspected Hypothyroidism

Forty-two tests were performed on 37 patients referred because of suspected hypothyroidism. Seventeen were done while the subjects continued to take thyroid, with doses as high as 0.256 gm. daily for two years before the test, whereas 25 tests were performed at a time when no thyroid had been taken for at least five weeks. Three of the 5 patients tested twice are included in Table 5, and the other 2 are discussed below.

The subject of Test No. 8 was a nine-year-old girl who had received thyroid since infancy for a diagnosis of cretinism made by a physician who had subsequently died. Since at the age of nine her only abnormality was a retardation of bone age of approximately two years (her I.Q. was 102, with a mental age of nine and a half years), a question concerning the correctness of the original diagnosis had been raised. The thyroid medication was withheld for two months, and studies were obtained. The TSH test clearly indicated a lack of thyroid activity, with no response to stimulation, and a basal metabolic rate of −31 per cent, with a serum

cholesterol of 401 mg. per 100 cc., was consistent with this. Thyroid therapy was therefore resumed, and her parents assured that she would need it the rest of her life.

One patient (Test No. 71) had previously had a subtotal thyroidectomy, and another (No. 77) had received I^{131} for hyperthyroidism. The serum PBI levels before and after TSH were 0.7 and 1.6 microgm. per 100 cc. in the former and 1.0 microgm. per 100 cc. and 0 in the latter. The results were consistent with an inadequate remnant of functioning thyroid tissue in each case. Both patients were subsequently much improved by thyroid medication.

The 3 patients whose tests comprised the last group were of considerable interest. One (Test No. 53) had had a subtotal thyroidectomy for a nontoxic diffuse goiter five and a half years previously, with intermittent symptoms of excessive fatigue and puffiness of the face subsequently. Determinations of the basal metabolic rate were as low as −27 per cent, but serum cholesterol levels were not elevated and several courses of thyroid produced only equivocal improvement. The PBI levels before and after TSH were 5.2 and 5.1 microgm. per 100 cc. respectively. Hence, the TSH test indicated that residual thyroid tissue was sufficient to show an initial PBI and three-hour uptake within the normal range, but the poor response to stimulation clearly demonstrated a lack of thyroid reserve. The remnant of the gland was already functioning at a maximum rate and hence could not respond to further stimulation. Two patients (Tests No. 13 and 76) had not had previous operations or I^{131} treatment. The former had noted chronic fatigue, brittleness of the nails, and some coarseness of the hair eighteen months previously, but she had been given thyroid without further studies. Since her response to this treatment was somewhat uncertain, the medication was later discontinued. Subsequent low basal metabolic rate and elevated serum cholesterol determinations were considered possibly due to withdrawal effect. The TSH test suggested a low thyroid reserve. PBI determinations were not performed with this test, but when done later while she was taking thyroid, they demonstrated no response. The patient in Test No. 76 had a history of excessive fatigue, drowsiness, metropathia and coarsening of the hair beginning four years previously. The basal metabolic rate was −21 per cent, but the serum cholesterol was not elevated and a trial with thyroid medication produced only questionable improvement, so that her symptoms were attributed to the menopause. Her PBI levels before and after TSH were 5.8 and 7.6 microgm. per 100 cc., respectively. Hence, although the I^{131} uptake suggested low thyroid reserve, the PBI response was normal, and it was assumed that the uptake response might have been obscured by exposure to iodine in a manner similar to that observed in the graduate nurse discussed above (Fig. 4). This test clearly demonstrated the necessity for determining PBI response to verify suspected low thyroid reserve.

The fact that Tests No. 13 and 53 had been reported an equivocal response to previous thyroid therapy stimulated a more careful review of the records. It was found that both patients had stated that they felt better while receiving thyroid medication, but some symptoms, which may well have had a neurotic basis, persisted, and the withdrawal of thyroid was not followed by a dramatic increase in the complaints. Hence it had been thought that the alleged improvement was probably psychogenic. The demonstration of low thyroid reserve enabled a definite diagnosis to be made after uncertainty for months or years in each case.

The subjects who were receiving thyroid at the time of their tests (Fig. 1) showed four types of response:

In 13 of the 17 tests, the response to TSH was definite, as in the known normal persons who were tested while receiving thyroid. The mean uptake by this group was 2.6 ± 2.4 per cent before TSH and 14.3 ± 7.4 per cent after TSH, with a mean increase of 11.7 ± 5.9 per cent. The thyroid reserve was obviously normal in spite of inhibition of the initial uptake by the medication.

One patient (Test No. 11, Table 5) had a low initial uptake with no response to stimulation, verifying the impression of hypothyroidism.

Two subjects (Tests No. 34 and 69 in Table 5 and indicated by broken lines in Figure 1) had an initial uptake within the normal range, with no increase after stimulation, suggesting low thyroid reserve. The patient represented by Test No. 34 had received I^{131} therapy for hyperthyroidism four and a half months previously, subsequently developing symptoms suggestive of hypothyroidism; the serum PBI levels before and after TSH were 3.3 and 3.6 microgm. per 100 cc., respectively. Test No. 69 was performed on the patient represented by No. 13 in Table 5; the PBI levels before and after TSH also showed no response. Hence, these tests are consistent with the presence of a remnant of thyroid tissue sufficient to cause a three-hour uptake within the normal range when stimulated maximally by endogenous TSH, but unable to supply enough thyroid hormone for normal requirements, as shown by the observation that even after the addition of small doses of exogenous thyroid the gland was being stimulated at a maximum rate and could not respond to further stimulation.

These three types of response correspond to those seen in patients who were not receiving thyroid at the time of their tests: normal subjects, patients with primary hypothyroidism and persons with low thyroid reserve. Test No. 65, however, reveals an entirely different picture. Although

this patient had been receiving 0.1 gm. of thyroid daily for four and a half years, her initial three-hour uptake was more than twice as high as that seen in any normal subjects, and this increased further after TSH stimulation. She was a nine-year-old girl who had been diagnosed as a cretin and started on thyroid at the age of six months. At the age of five, an enlargement of the thyroid gland was noted, and withdrawal of medication for three months resulted in marked sluggishness and somnolence, with a rise in serum cholesterol to 701 mg. per 100 cc. Resumption of thyroid relieved the symptoms and restored the serum cholesterol level to normal. At the age of nine, when the TSH test was performed, she still had a goiter and her bone age and mental development were also somewhat retarded in spite of therapy. The TSH test demonstrated that there was no defect in the ability of the thyroid gland to trap iodine and that this function could apparently respond further to TSH administration; hence there must have been an inability to utilize this iodine to form thyroid hormone. To clarify this point further the test was repeated with determinations of PBI as well as of I^{131} uptakes. This time the uptake was 49.4 per cent before and 53.3 per cent after TSH; the PBI was 2.2 microgm. per 100 cc. before and 2.9 microgm. after TSH. The failure of the PBI to rise significantly confirms the impression that this patient's thyroid gland was unable to utilize iodine to form thyroid hormone. Furthermore, the finding of an elevated uptake of I^{131} and low initial PBI in spite of 0.1 gm. of thyroid daily suggested that this dosage was inadequate and that it should be increased.

Others have reported a few cases of cretinism with goiter in which a defect in ability to utilize iodine to form thyroid hormone was apparently present. Hamilton and his associates[11] referred to 2 patients whose thyroid glands took up abnormally large amounts of radioactive iodine and who were clearly not deficient in iodine. Lerman, Jones and Calkins[12] noted 2 similar patients whose glands took up large quantities of radioactive iodine, but histologically their thyroid tissue showed a low concentration of protein-bound iodine and areas of intense hyperplasia. Stanbury[13, 14] studied 4 additional cases and noted that the I^{131}, which was concentrated avidly by their thyroid glands, was released rapidly after administration of thiocyanate, suggesting that the glands were unable to utilize it. The demonstration that the case represented by Test No. 65 in this study had an elevated control uptake of I^{131} but no appreciable response in the low level of serum PBI to TSH is additional evidence that the defect in such cases must lie in an inability to utilize iodine to form thyroid hormone.*

It is interesting that despite the depressed initial uptake in the patients with questionable hypothyroidism who responded normally to TSH in this group, the response was not significantly different from that seen in known normal persons not receiving thyroid. This observation suggests that there is no impairment of the ability to respond to TSH after prolonged intake of thyroid and is consistent with the findings of Perloff et al.[5] and Perlmutter and his associates,[6] who also demonstrated little difference in response of I^{131} uptake to TSH whether subjects were on or off thyroid medication.

Side-Effects of the Test

In the 132 tests performed to date there have been no serious untoward reactions to the injection of TSH, 20 mg. having been the largest dose employed. Side effects have been minimal. In 1 case tenderness over the thyroid gland was noted on the second test day. In another, a transient mild urticaria developed about two hours after the injection and cleared spontaneously two hours later. Both these subjects received 20 mg. of TSH preparation No. J 13903-R, which was somewhat less purified than No. K 46808-R, the lot used in most of the tests; the only side effect observed with the latter has been occasional mild pain at the site of injection.

Discussion

The availability of thyrotropic hormone in a preparation suitable for administration to human beings has made it possible to determine the capacity of a thyroid gland to respond to stimulation. The studies presented in this report indicate to some extent the value of this development in clinical medicine.

The finding that a single intramuscular injection of a comparatively small dose of TSH produces a significant increase in the uptake of radioactive iodine by the thyroid gland has been used as the basis for a test that can be performed in any laboratory equipped to handle this radioactive isotope. The technic is so simple that it takes little more time and requires no more technical training than an ordinary twenty-four-hour uptake test. Preliminary observations suggest that determinations of serum protein-bound iodine may be followed instead of, or in addition to, I^{131} uptake but the more complicated nature of this chemical determination and its less general availability will probably result in its being reserved for special circumstances, such as verification of low thyroid reserve.

The test used in this clinic has been found to be both safe and practical. Since it involves only a

*Since the preparation of this manuscript, two interesting reports of I^{131} studies on cases of cretinism with goiter have appeared.[15, 16] Their findings indicate that some goitrous cretins can produce thyroxin, although probably in inadequate amounts, and others can produce an iodinated protein but no thyroid hormone. An increased avidity of the thyroid gland for iodine was apparently present in all cases. Hence it appears that cretinism with goiter may result from a defect at more than one stage in the formation of thyroid hormone, and that this defect may be relative rather than absolute.

single injection of 10 mg. of TSH, side effects have been negligible and the danger of development of antihormone effect is minimal. To date the test has been performed twice on 7 persons and three times on 1 without evidence of decrease in TSH effect. The utilization of small tracer doses of I^{131} also enables judicious repetition of the test without danger of excessive radiation. Since it can be conveniently performed on an outpatient basis, its applicability is greatly increased.

The greatest clinical advantage of the test is its ability to determine the potential capacity of the thyroid gland to respond to stimulation even during the administration of thyroid. In this respect it is unique among tests of thyroid function. Through its application one can readily clarify a questionable diagnosis of hypothyroidism.

Its use has also revealed a type of thyroid dysfunction that has not hitherto been clearly recognized — low thyroid reserve. This condition is characterized by the presence of an amount of thyroid tissue that is almost, but not quite, capable of supplying thyroid hormone sufficient to meet physiologic requirements. The borderline nature of the deficiency makes it extremely difficult to diagnose by clinical observation or customary tests of thyroid function. As would be expected, it occurs most frequently in patients who have previously received subtotal thyroidectomy or radioactive iodine therapy, but it may occur spontaneously, possibly as an early phase in the development of frank hypothyroidism or myxedema.

The TSH test has also thrown more light on the nature of the defect in thyroid function in a case of cretinism with goiter. The finding of an elevated uptake of I^{131} in the presence of obvious deficiency of thyroid hormone and a lack of appreciable response of serum PBI to TSH fits very well with the concept of Stanbury[13, 14] that such patients must have an inability to utilize iodine in the formation of thyroid hormone.

The test has certain obvious limitations. Since exposure to inorganic iodide alters the uptake of I^{131} by the thyroid gland, the response to TSH stimulation is obscured under such conditions unless serum protein-bound iodine levels are followed. If a question of exposure to iodine is present and serum PBI determinations are not available, the test should not be performed until an interval of at least six to eight weeks has elapsed after the last contact with iodide. Since organic iodides, such as x-ray contrast mediums, invalidate serum PBI determinations as well as I^{131} uptake, a suitable interval after the administration of these substances must also be observed before the test can be performed. Another situation in which the test would not be feasible is the period after administration of a comparatively large dose of a gamma-emitting radioactive isotope during which radioactivity in the thyroid gland or other tissues would obscure that originating from the tracers used in the test.

In the presence of substernal thyroid tissue or struma ovarii, although measurements of absolute uptake of the small tracers would not be accurate, the response to TSH could still be determined by the difference between the three-hour uptakes and the serum PBI's.

Finally, it should be remembered that a good response in itself does not rule out the possibility of hypothyroidism secondary to deficient stimulation by the pituitary gland. If patients with this condition are not receiving thyroid, a low initial level of I^{131} uptake or serum PBI should differentiate them from normal persons.

Summary and Conclusions

A single injection of 10 mg. of a relatively pure preparation of thyrotropic hormone produces a significant increase in the three-hour uptake of small tracer doses of I^{131} on successive days. This effect has been used as the basis of a comparatively simple test for determining the ability of the human thyroid gland to respond to stimulation. The advantages and limitations of this test are discussed. Preliminary observations indicate that in certain cases in which I^{131} uptake may be obscured, determinations of serum protein-bound iodine may be helpful.

Experience with the test indicates that it affords an effective means for determining the presence of obscure hypothyroidism, even during the administration of thyroid, and its use has revealed a type of thyroid dysfunction that has not hitherto been clearly recognized — low thyroid reserve. Its application in the study of a case of cretinism with goiter demonstrated a defect in the ability of the thyroid gland to utilize iodine to form thyroid hormone.

In addition to its obvious clinical applications, such a test also promises to be helpful in the study of thyroid function under various conditions.

We are indebted to Dr. Arthur S. Littell for advice and assistance in the statistical evaluation of the data, to Jean Baller and Paul Anthony for technical assistance in the determination of I^{131} uptakes and to Daniel Leb, Mrs. Georgia James, Loretta Langen, Lynn Donelan and Suzanne Rankin for technical assistance in the determination of serum PBI's.

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FRACTURES OF THE CARPAL NAVICULAR

Accurate Diagnosis and Planned Treatment

CAPTAIN EDWARD C. BRANSON, M.C., U.S.A.*

HEALING and return of completely useful wrist function after fractures of the proximal half of the carpal navicular depend almost entirely on the adequacy of treatment. This conclusion is based on 32 cases treated at the Fifth General Hospital, United States Army, in which the period of observation has been at least six months and in many cases as long as two years.

To be successfully treated this injury must be correctly diagnosed early. Positive diagnosis is possible only with adequate x-ray examinations. Every wrist injury with hyperextension must be considered a fractured navicular until the contrary is proved by x-ray examination. Any such injury that remains painful for longer than two weeks is probably a fracture. Navicular fractures are not always visible on the usual anteroposterior and lateral wrist views; oblique views are necessary. Practically all navicular fractures can be seen on either an anteroposterior or on an ulna oblique view. However, regardless of the x-ray views used, every navicular fracture cannot be definitely demonstrated at the time of injury. A few can be seen clearly only after calcium absorption has had time to occur along the fracture line. Sufficient absorption to render the fracture line visible usually occurs within two to four weeks of injury. In this group of 32 fractures, 2 that could not be demonstrated at the time of injury were seen clearly four weeks later. In a third case, examinations over a period of two months did not confirm the fracture suspected on x-ray study at the time of the injury. Four cases were interpreted by the radiologist at the initial examination as "probably incomplete fractures." Subsequent x-ray films after intervals of two to six weeks revealed that 2 of these were, in fact, complete fractures. These required three and a half and four months to heal. The 2 that could not be proved to be complete fractures required two and a half months to heal. It is probable these were complete fractures and that the entire fracture line was never demonstrated. All so called "incomplete" navicular fractures should be considered complete fractures inadequately visualized and treated by immobilization until healing has occurred (Fig. 1).

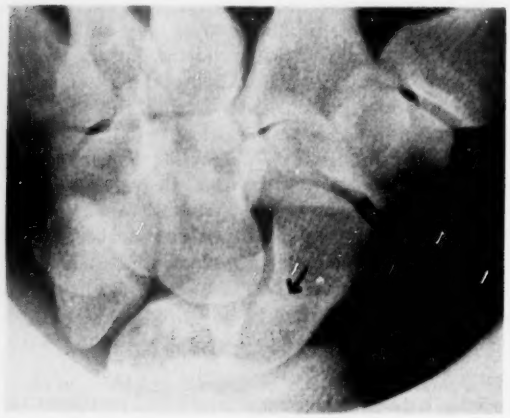

FIGURE 1. *Typical "Incomplete Navicular Fracture." This wrist must be immobilized. Incomplete fractures are usually complete fractures incompletely visualized.*

With adequate immobilization practically all navicular fractures will heal. Without immobilization bony union does not occur. Adequate immobilization implies as complete immobilization as possible, continued until x-ray evidence of healing has been demonstrated. Motion at the fracture site undoubtedly delays or prevents union. This is proved by the almost invariable failure of union to occur in cases not immobilized and by cases in which the fracture line becomes more evident after removal of the cast for one or two weeks. Therefore, complete immobilization is the key to success in the treatment of this injury.

A cast that includes the distal three fourths of the forearm and first metacarpal phalangeal joint is necessary. Various positions of the wrist and the first carpo-metacarpal joint have been advocated to impact and maintain immobilization of the fracture fragments. Friedenberg,[1] on the basis of x-ray studies, concluded that a position of 30° dorsiflexion

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and mild radial deviation of the wrist gives the best approximation of the navicular fragments. The position of function of the wrist and thumb has been used in this series. This is approximately the position suggested by Friedenberg.[2, 3] The functional position, by permitting use of the hand, reduces the amount of atrophy from disuse.

The cast must fit well. It must be skin tight. Small plaster splints should be used at the base of the thumb, at the distal flexion crease of the palm and at the interphalangeal joint of the thumb. These reinforce the cast at the points at which breaking most frequently occurs. Because the functional position does not eliminate atrophy of disuse, it is recommended that the cast be changed every six weeks. More frequent changes give an unnecessary opportunity for damaging motion at the fracture site, probably prolonging the time required for healing.

Early immobilization is strongly recommended even though the x-ray diagnosis may be equivocal. It is my impression that the period required for healing has been materially lengthened in cases in which casting has been delayed for more than one or two weeks after injury. Healing is not likely if immobilization has been delayed more than three months. X-ray examination is the only accurate method of

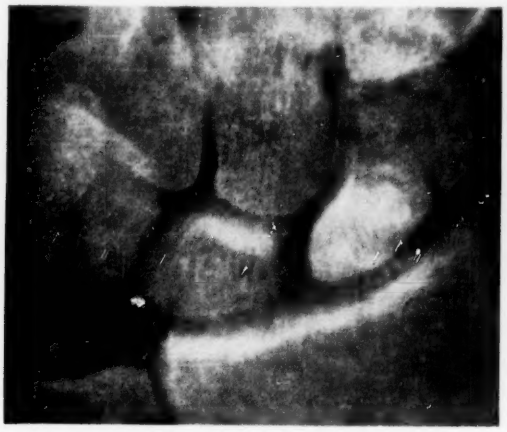

FIGURE 2. *Fracture of the Proximal Half of the Navicular Four Months after Injury.*
The fracture line is blurred; the middle third of the fracture line shows questionable union. Aseptic necrosis is established.

determining the progress of healing. At the time the cast is changed every six weeks, anteroposterior, lateral and ulna oblique views should be taken. Bone trabeculae crossing the fracture line should be the x-ray criterion for healing; a blurred fracture line without this criterion is not sufficient evidence of healing. When healing has been demonstrated by x-ray examination, two weeks of full use of the wrist without a cast or leather support is permitted. At the end of this time x-ray examination should be made.

In this series of 32 cases there were 2 that were thought to be healed; however, on x-ray study two weeks after removal of the cast the fracture line was again seen quite clearly. An additional period of immobilization of three months in 1 case and four months in the other was required before union was definitely established. Absorption or refracture of the callus from the strain of normal wrist motion apparently occurs in a small number of cases.

X-ray findings of relatively increased density of the proximal fragment or cystlike changes in the proximal fragment indicate aseptic necrosis. These changes are due to impairment or loss of the blood supply to the proximal fracture fragment. As healing occurs new blood vessels grow across the fracture line from the distal fracture fragment, and revascularization of the necrotic bone occurs. During this period of revascularization and bone healing, the proximal pole of the navicular is soft and friable. Bony union at the fracture line usually does not

FIGURE 3. *Healing of Fracture Line Eight Months after Injury. (Same Patient as Figure 2.)*
Relative increased density of the proximal pole and cystic change indicate aseptic necrosis. Immobilization must be continued.

occur until healing of the aseptic necrosis is well advanced. If the line of fracture appears to be healed and evidence of aseptic necrosis remains in the proximal pole of the navicular, immobilization must be continued until healing of the aseptic necrosis is complete; otherwise, the friable proximal pole of the navicular will collapse under the strain of normal wrist use, and a compressed, deformed articular surface of the proximal navicular will result. In 1 patient in this series aseptic necrosis of the proximal pole was still evident eleven months after the immobilization was begun (Fig. 2). The fracture line had healed eight months after the injury (Fig. 3).

Healing occurred in 30 of these 32 cases. One patient, who was not immobilized until two months after the injury, appears to have a definitely established nonunion. He has been immobilized for

fourteen months. Immobilization should be continued since healing has been reported after as long a period as twenty-four months.[4] The second patient in whom healing has not occurred appears to have bony union across the fracture line; immobilization is being continued until healing of the aseptic necrosis occurs. Eventually, this case can probably be listed as healed. Healing has been established by x-ray in 8 cases within less than four months of immobilization. Eighteen cases required four to six months for healing, and 6 cases, including the 2 that have not healed, were immobilized for longer than six months. There is no serious disability of the injured wrists in any patient in whom healing has occurred. Three patients have approximately 20° limitation of dorsiflexion, and all 3 complain of mild pain after heavy work with the wrist. With these exceptions the results, including wrist strength, range of motion and freedom from pain, have been good.

Summary and Conclusions

Accurate diagnosis of carpal navicular fractures is possible only by x-ray studies using multiple projections of the wrist.

Immobilization of the distal three fourths of the forearm, wrist and the first metacarpal phalangeal joint in a skin-tight cast with the wrist, and thumb joints in the position of function, is recommended. Immobilization should be continued until bony union of the fracture has occurred and aseptic necrosis of the fracture fragments has healed.

An x-ray examination should be done two weeks after the cast has been removed. If the fracture line has become more evident, healing is not complete, and recasting is indicated.

In a series of 32 fractures of the proximal half of the carpal navicular treated in this manner, healing occurred in 30 cases, or 93 per cent. Eight fractures, (25 per cent) healed in less than four months; 18 fractures (56 per cent) required between four and six months for healing, and 6 (19 per cent) required over six months of immobilization. Two of these 6 patients have been immobilized more than six months, without healing.

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THE RESPIRATORY DEPRESSANT ACTION OF N-ALLYLNORMORPHINE IN THE NORMAL SUBJECT AND IN PATIENTS WITH RESPIRATORY ACIDOSIS SECONDARY TO PULMONARY EMPHYSEMA*

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N-ALLYLNORMORPHINE (Nalline), a substance that has been amply shown to counteract the respiratory depression caused by morphine and related compounds, has received little attention as a respiratory depressant in its own right. Eckenhoff et al.[1] demonstrated in 5 normal subjects that Nalline alone caused depression in respiratory minute volume but had little effect on the rate of breathing. This observation is important in the light of the recent suggestion that Nalline may be useful in combating the respiratory depression in severe respiratory acidosis not related to drug intoxication.[2]

Table 1. *Ventilation Measurements in Normal Subjects.*

Subject	Control Value							
	Room air†		100% O_2		2.8% CO_2		4.3% CO_2	
	vol.*	rate	vol.	rate	vol.	rate	vol.	rate
1	6.9	9.2	6.5	9.6	13.8	13.2	16.8	14.0
2	5.4	7.8	6.6	10.0	16.3	11.8	23.7	12.0
3	6.1	17.6	4.9	16.6	7.8	14.4	13.6	21.6
4	6.8	11.0	7.4	12.0	14.4	11.4	20.6	12.4
Mean	6.3	11.4	6.3	12.1	13.1	12.7	18.7	15.0

*Liters per min. B.T.P.S. expired volume.
†Per minute.

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The present report is an analysis of the respiratory effects of small doses of this drug in normal subjects and patients with respiratory acidosis secondary to severe pulmonary disease alone. Par-

ticular emphasis has been placed on measuring the change in sensitivity of the respiratory center to carbon dioxide by stimulus-response curves for each subject before and after the administration of N-allylnormorphine.*

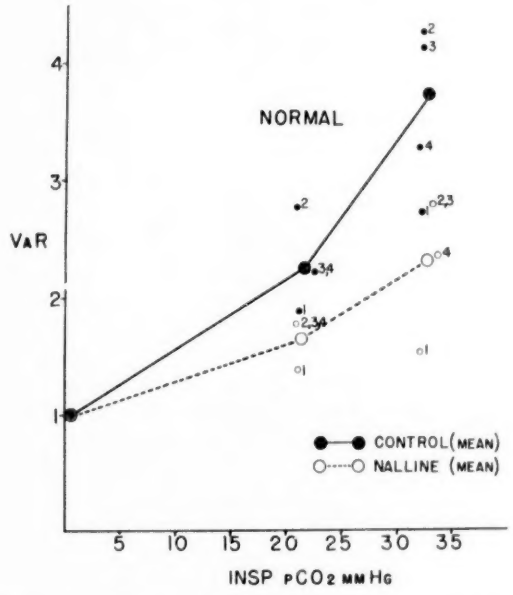

FIGURE 1. *Ventilation Response to Carbon Dioxide in the Normal Subject.*

Ordinate = alveolar ventilation ratio (V_AR), and abscissa = inspired carbon dioxide. The small solid dots indicate the individual control values for the normal subjects numbered according to Table 1. The open circles are similarly the individual values after Nalline.

nected to a Statham air-strain gauge and carrier-wave amplifier recorded the chest movements continuously to measure respiratory rate.

The subjects breathed the various gas mixtures for fifteen-minute intervals each, but the mean minute volume and rate for the last five minutes only were used in the calculations. Room air, 100 per cent oxygen, 2.8 per cent carbon dioxide in oxygen and 4.3 per cent carbon dioxide in oxygen were the test mixtures used. The difference between room air and 100 per cent oxygen provided a rough index of the force of the hypoxic drive, and the carbon dioxide mixtures allowed an evaluation of the pure carbon dioxide effect since the oxygen concentration in these mixtures would elevate the alveolar oxygen tension far above threshold values. Alveolar ventilation was calculated from the measured minute volume and rate (alveolar ventilation = expired minute volume − dead space x rate), assuming a constant dead space of 150 cc. Although this value is probably too small for the diseased sub-

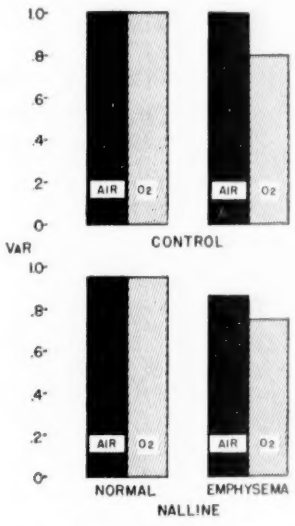

FIGURE 2. *Change in Alveolar Ventilation Ratios (Mean Values) on Breathing of 100 per cent Oxygen before and after Nalline.*

TABLE 1 (*Concluded*).

SUBJECT	AFTER NALLINE ADMINISTRATION							
	ROOM AIR		100% O_2		2.8% CO_2		4.3% CO_2	
	*vol.**	*rate†*	*vol.*	*rate*	*vol.*	*rate*	*vol.*	*rate*
1	6.1	9.2	6.0	9.8	9.2	11.8	10.6	12.8
2	7.2	8.2	7.7	9.2	10.7	9.2	15.9	11.0
3	5.1	15.2	4.8	14.6	6.8	15.8	9.5	17.2
4	6.5	10.2	6.4	12.4	12.1	13.8	15.6	13.6
Mean	6.1	10.7	6.1	11.5	9.7	12.6	12.9	13.7

METHODS

All measurements were made while the subject was seated comfortably in a canvas chair. A mouthpiece was connected to a two-way valve with the inlet from a Douglas bag and the outlet to a low-resistance gas meter. A chest pneumograph con-

*Kindly supplied by Merck and Company, Rahway, New Jersey.

ject, the resulting calculation will give high values for their alveolar ventilation and will actually minimize any depressant effect present after drug administration. We calculated alveolar ventilation ratios (V_aR) for the oxygen effect by assigning the control resting alveolar ventilation on room air a value of 1. The ratios for the carbon dioxide effect were calculated on the basis of a value of 1 in each subject for his alveolar ventilation while breathing pure oxygen without Nalline.

Four healthy young adult males served as the control subjects. Four patients with pulmonary emphysema were studied. Of these, 1 had no significant respiratory acidosis and responded to Nalline like the normal subjects. The other 3 (2 males and 1 female) were in varying degrees of respiratory acidosis. Subjects T.J. and C.C. had been followed for several years with obstructive emphysema, and the former had been carried on pneumoperitoneum for two years. Both were chronically cyanotic and had plasma carbon dioxide contents of 30 and 37 milliequiv. per liter, respectively. Subject E.B. was chronically ill with pulmonary emphysema and had recently recovered from a superimposed pulmonary infection and congestive heart failure at the time Nalline was administered; her venous carbon dioxide content was 34 milliequiv. per liter.

The Nalline was given intravenously in all subjects, and measurements were begun immediately. Subjects M.T., D.H., M. and C.C. received 2 mg.; subjects T., T.J., and E.B. received 10 mg.

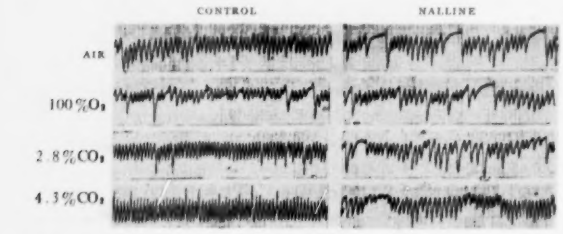

FIGURE 3. *Chest Pneumograms from Subject T. J. during Ventilation Testing (Note the Periodic Breathing on All Gas Mixtures after Nalline).*

RESULTS

Normal Subjects

In 3 subjects Nalline diminished the minute volume of respiration on air without any significant change in rate. In 1 subject minute volume increased slightly. The measured volumes for the 4 subjects are shown in Table 1. The calculated alveolar ventilation during carbon dioxide breathing decreased in all subjects after Nalline. The mean decrease for the 2.7 per cent carbon dioxide in oxygen mixture was 3.4 liters per minute, and that for 4.7 per cent carbon dioxide in oxygen was 5.6 liters per minute. Furthermore, when a stimulus-response curve is drawn (Fig. 1) for the carbon dioxide effect, the control curve is seen to have an inflexion point at about 20 mm. of mercury, and the general shape coincides well with similar curves in the literature for normal subjects.[3] The curve after Nalline has a less well defined inflexion point, which is displaced to the right. Since the slopes of these curves are indicative of the increase in ventilation for each increment increase in inspired carbon dioxide they constitute a measure of the sensitivity of the respiratory center for the carbon dioxide (and ? H^+) stimulus. This value may be calculated for that part of the curve in the test range of carbon dioxide mixtures used — that is, from 22 to 33 mm. of mercury of inspired carbon dioxide. For the control curve the mean value is 0.13 (change in V_aR for each 1 mm. increase in inspired carbon dioxide within the range specified) whereas for the same subjects after Nalline it is 0.059, indicating a decrease of roughly 50 per cent in sensitivity to carbon dioxide.

Figure 2 shows the alveolar ventilation ratios before and after breathing of pure oxygen. There is no change in the normal subject under Nalline.

TABLE 2. *Ventilation Measurements in Patients with Emphysema.*

SUBJECT	CONTROL VALUE							
	ROOM AIR		100% O_2		2.8% CO_2		4.3% CO_2	
	*vol.**	*rate†*	*vol.*	*rate*	*vol.*	*rate*	*vol.*	*rate*
T.J.	10.4	11.4	8.2	12.8	16.2	16.0	20.5	16.0
C.C.	8.8	12.8	8.0	12.6	9.2	10.6	10.8	16.4
E.B.	12.3	33.5	10.7	32.2				
Mean	10.5	19.2	9.0	19.2	12.7	13.3	15.7	16.2

*Liters per min. B.T.P.S. expired volume.
†Per minute.

Patients with Respiratory Acidosis Secondary to Pulmonary Emphysema

The data on 3 subjects with chronic respiratory acidosis are presented in Table 2. Their ventilation was increased above normal while they were breathing room air at rest. The fall in ventilation that occurred with breathing of 100 per cent oxygen indicates an abnormal degree of hypoxic drive characteristic of such patients (Fig. 2).

The effect of Nalline on ventilation in the presence of a hypoxic drive (that is, while breathing room air) was studied in 2 subjects. In both, the alveolar ventilation was diminished by the drug.

A similar depression was observed in 2 subjects given Nalline while breathing 100 per cent oxygen. In the third subject under these conditions there was a 10 per cent increase in alveolar ventilation.

with emphysema experienced a period of frank delirium.

Effect of Nalline in Acute Carbon Dioxide Narcosis

To evaluate any possible respiratory stimulant effect of Nalline when there is true narcotic depression from carbon dioxide, rather than simply a decreased responsiveness to this gas as shown in

TABLE 2 (*Concluded*).

SUBJECT	ROOM AIR		AFTER NALLINE ADMINISTRATION 100% O_2		2.8% CO_2		4.3% CO_2	
	vol.	*rate*	*vol.*	*rate*	*vol.*	*rate*	*vol.*	*rate*
T.J.	6.8	9.0	8.5	10.4	10.9	9.8	14.6	15.0
C.C.	9.3	20.0	6.6	17.8	8.8	18.2	10.4	21.1
E.B.			7.6	28.5				
Mean	8.1	14.5	7.6	18.9	9.9	14.0	12.5	18.1

All subjects showed marked changes in respiratory rhythm when given Nalline. The chest pneumograms from patient T.J. are illustrated in Figure 3 to show the periodic breathing that became manifest after Nalline even when the subject was breathing 4.3 per cent carbon dioxide. Although the over-all rate change was slight these periods of profound tidal depression really amount to apnea so far as alveolar ventilation is concerned since little more than the dead space is ventilated.

The emphysematous subjects, during the control period, showed decreased sensitivity to elevations in inspired carbon dioxide as compared to the normal subjects (Fig. 4). With the concentrations of carbon dioxide used, no inflexion is apparent, and the points describe well a straight line. In addition to this decreased sensitivity it is apparent that the responsiveness is still further decreased after Nalline. Calculated as in the normal subjects the individual changes in the ventilatory response curves to carbon dioxide (22 to 33 mm. of mercury) for the control and Nalline test periods are as follows: subject T.J., 0.052 (increase V_aR per 1 mm. of mercury increase inspired carbon dioxide) control and 0.035 Nalline; and subject C.C., 0.026 control and 0.017 Nalline. Both had a decrease in responsiveness to carbon dioxide of 33 per cent after Nalline — approximately the same as in the normal subjects. Considering that these patients had already shown, in the control period, a marked insensitivity to carbon dioxide, the inherent danger from further depression by Nalline is only too obvious.

The subjective experience of all, normal and diseased, followed a similar pattern within a few minutes of the injection of Nalline. This was characterized by a feeling of drowsiness and general indifference, likened by most to the effects of a moderate amount of alcohol. One of the patients

the subjects with emphysema, simple experiments were performed on 3 mongrel dogs. The animals were lightly anesthetized with pentobarbital sodium, tracheotomized and allowed to breathe 100 per cent oxygen through a two-way valve for thirty minutes. By the end of this time they were practically denitrogenated and were then connected through a

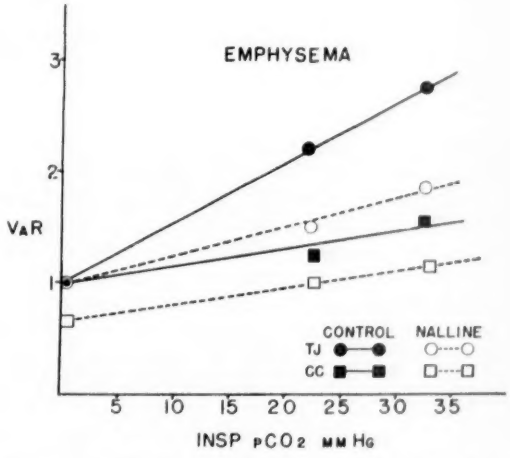

FIGURE 4. *Ventilation Response to Carbon Dioxide in Respiratory Acidosis (Plotted As in Figure 1).*

closed circuit to a spirometer with carbon dioxide absorber removed and containing 30 per cent carbon dioxide and 70 per cent oxygen. Tidal volume and respiratory rate promptly increased, and the animal was kept on the closed system rebreathing the gas mixture, and thus continuously raising its carbon dioxide content. This was continued to the arbitrary point of respiratory depression de-

fined as the time when the respiratory minute volume had fallen to half its peak value. At this point the carbon dioxide in the spirometer was analyzed (mean value was 40 per cent), and 2 mg. of Nalline was given intravenously. This dose had no effect in any animal on either tidal volume or rate. Two minutes later 4 mg. was administered, and again no effect was apparent. Similarly, morphine and Nalline when given together exerted no stimulating action in the presence of true carbon dioxide narcosis.

Discussion

The experiments reported here support and amplify the observations of Eckenhoff et al.[1] that Nalline in normal man is a respiratory depressant, even in small doses. The importance of relating alveolar ventilation instead of expired minute volume to an increasing carbon dioxide stimulus is apparent in a subject like C.C., who showed a slight increase in expired volume but nearly doubled his rate on room air after administration of Nalline. Although this might superficially appear to be a stimulant effect, the result is simply a greater dead-space ventilation and actual fall in alveolar ventilation. Our experiments do not support the suggestion that this drug may be of benefit in respiratory acidosis not related to drug intoxication, nor do they support the contention that its primary mechanism of action is as a stimulant of the central nervous system, especially the respiratory center.[2]

Summary and Conclusions

N-allylnormorphine (Nalline) is a potent respiratory depressant in the normal subject and in the patient with chronic pulmonary disease who has respiratory acidosis unrelated to drug intoxication. This drug lowers the sensitivity of the respiratory center to carbon dioxide approximately 50 per cent.

In the dog with acute respiratory depression from carbon dioxide narcosis the drug has no effect on ventilation.

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MEDICAL PROGRESS

WAR WOUNDS*

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THE care of war wounds in these days of conflict and world tension is of vital concern to all in the field of medicine. Accordingly, this communication has been prepared to give a progress report on the current care of the wounded of war. When one views the prospects of full-scale hostilities in the Atomic Age, the enormity and gravity of the situation that confronts all physicians, civilian and military alike, is staggering. It has seemed appropriate that this paper should consider the following subjects: lessons learned in World War II, that have been relearned through experience in the Korean War; the true advances that have been made in the care of war wounds since World War II (much of this progress has resulted from intensive study of physiologic derangements in battle casualties carried out both in this country and in Korea, the investigations in Korea being extended even to the men in the advance outposts who are in constant contact with the enemy); and the problems peculiar to the care of the war wounded that still confront the medical service.

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Organization of the Medical Service

In contrast to civilian practice, in which the patient is usually treated from wounding to rehabilitation by a single surgeon or a group in one hospital, the treatment of the battle casualty is carried out by many surgeons of different backgrounds and levels of experience in a large number of installations that are often widely separated. Furthermore, military surgery is characteristically concerned with trauma of epidemic or endemic proportions in young, previously healthy persons in whom the violence of the trauma far exceeds that usually encountered by civilian surgeons. Soldiers in combat must be removed from the place of wounding over terrain that is often difficult to points where treatment can be initiated. The time lag between injury and treatment will vary with the tactical situation. After the initial surgical treatment the wounded man must be evacuated to the rear for subsequent care to keep pace with the flow of casualties from the front. As a consequence, military surgical procedures of necessity are simple and standardized and are based on sound surgical principles derived from previous war experience.

In Korea the system of evacuating the wounded man from the field of battle to a medical installation has undergone some changes from the pattern employed in World War II. As previously, the average casualty continues to be seen first by the company aid man, who applies an emergency dressing and other first-aid measures. He is then evacuated by walking, litter or jeep ambulance to the battalion aid station, which is usually located at the most forward limit of road transport. Here, rapid assessment of the severity of the wound to determine which wounds take precedence in treatment, establishment and maintenance of an adequate airway, control of hemorrhage, initiation of blood, water and electrolyte replacement, immobilization and dressing of wounds, relief of pain and initial antibiotic therapy for suppression of bacterial growth are accomplished. Importance of the rapidity and thoroughness with which these measures must be carried out is reflected by the current policy of orienting newly assigned battalion surgeons at clearing stations and forward hospitals before assignment to the aid station to give them additional training in resuscitation, a sounder concept of what treatment is available in these centers and acquaintance with the officers who administer it. This policy has the additional advantage of giving the officer the opportunity to become accustomed to field conditions before he accepts the responsibility of an aid station. The battalion surgeon, in turn, provides additional training for his aidmen in assessing the severity of wounding, in the early recognition of wound shock, in deciding when and how to give morphine, and in the factors that govern priority and manner of evacuation.

Changes have occurred in the method of moving patients from the battalion aid station. An important advance has been made by the introduction of the helicopter. This can be landed in terrain not accessible to the jeep and provides a rapid means of transportation. Helicopter evacuation has resulted in by-passing the clearing station for first priority casualties and delivering them directly to the army surgical hospital. The less injured go to the division clearing company, where minor débridements may be performed, or are sent on to the evacuation hospital. In Korea each one or two divisions in combat are now supported by a surgical hospital instead of a platoon of a field hospital. The hospital is equipped with 60 or more beds and receives all types of battle casualties. Two of these hospitals have neurosurgical teams. Definitive initial surgery is performed at this level. The evacuation hospital is the next link in the chain. In Korea the evacuation hospital currently functions primarily to care for medical casualties, to receive the overflow from the surgical hospitals and to serve as a triage point between the surgical hospitals and the general hospitals in Japan. At night and during adverse weather when the helicopter cannot fly, the medical officer must decide which casualties are to be held overnight or until the weather clears and which are to be sent on by jeep, ambulance or hospital train. When the casualty load is not heavy, the helicopter may be used to evacuate those with less serious wounds. Patients able to be moved and needing further care are evacuated to general hospitals in Japan for definitive treatment, usually by air and less frequently by hospital ship. Wounded not likely to return to duty are evacuated for further care to hospitals in the United States.

Priority of surgical intervention is as follows:

First priority (mechanical correction of defects that immediately endanger life): control of external hemorrhage; relief of increasing intracranial pressure (hematoma); control of internal hemorrhage; relief of respiratory obstruction and closure of sucking chest wound; maintenance of adequate airway; and relief of cardiac tamponade.

Second priority (correction of defect that ultimately endangers life): definitive repair of perforations of gastrointestinal tract, genitourinary tract or biliary-pancreatic tract; débridement of cerebral wounds; relief of progressive spinal-cord pressure; exploration of wounds of mediastinum; and surgical amputations after traumatic amputation (to control bleeding and prevent sepsis).

Third priority (correction of defect that immediately endangers limb or organ): Repair of major arterial wound.

Fourth priority (correction of defect that ultimately endangers limb or organ): exploration of ocular injuries; and immobilization of compound fractures and reduction of dislocated joints.

Fifth priority: débridement of soft tissues and realignment of fractures.

Delayed operation: Closure of soft-tissue wounds and repair of peripheral nerves.

Wounds

Classification

Traumatic wounds are either open or closed. This distinction is made on the basis of the integrity of the overlying skin and mucous membranes. Open wounds are, of course, more likely to become complicated by infection. However, even in apparently closed wounds, damaged tissues and hematomas afford a favorable medium for colonization with contaminating bacteria from minute breaks in the skin or from blood-borne organisms. Open wounds, according to the classification of Churchill,[1] may be either simple or complex. Open wounds are classified as simple when the injury is confined to the skin, subcutaneous tissue or fascia, muscle damage being absent or minimal. When deep muscles are injured not only does the wound become complex but also the patient presents the special hazard of vulnerability to severe hemorrhage, wound shock and serious infection. Finally, wounds

may further be classified as penetrating or perforating, depending on whether or not the wounding agent has traversed the tissues completely and created a wound of exit.

Regional Distribution

Data for the wounded in action from Holmes' study,[2] in rough agreement with data from other wars,[3, 4] in the Korean action are distributed as follows: head, 16 per cent; thorax, 8 per cent; abdomen, 6 per cent; upper extremities, 26 per cent; and lower extremities, 44 per cent. Head and thoracic wounds account for over 50 per cent of those killed in action or dying subsequently; thoracoabdominal and abdominal wounds are next in order of lethality, whereas the fewest deaths result from injuries to extremities. This survey indicates a regional wound incidence per casualty of about 2. The mortality rate is related to the number of wounds, particularly of the thorax and abdomen, since the rate almost doubles if more than one wound is present.

The incidence of penetrating wounds is greater than that of perforating wounds, the ratio for the various regions being as follows: head, 15:1; thorax 8:1; abdomen, 4:1; and extremities, 3:1. It may be noted that the preponderance of penetrating wounds diminishes with injuries farther from the head.

Causal Agents

One analysis of wounds in the Korean campaign demonstrated the following incidence of causal agents: mortar wounds, 37 per cent; bomb and grenade wounds, 21 per cent; gunshot wounds, 17 per cent; shell and high-explosive wounds, 12 per cent; mines, 6 per cent; battle accidents, 6 per cent; burns, 1 per cent. This distribution is not unlike that seen during certain periods of the latest war in Europe. The risk of burns in battle has increased steadily over the last fifty years, and the low proportion of burns in this list may be seasonal. Accidental napalm burns have shown no clinical differences from burns of equal severity due to other agents, such as phosphorus and gasoline, and the full thickness of the skin has not been invariably destroyed.

Body Armor

The modern care afforded the wounded reaching hospitals, although culminating in a progressive lowering of the mortality rate, has coincided with a corresponding increase in the lethality of weapons. Therefore, the ratio of killed in action to wounded in action before Korea has remained essentially unchanged. For this reason, efforts have been made since World War II to develop and use body armor to protect the body from missiles. The decreased incidence and severity of head injuries associated with the wearing of a steel helmet is well known. In the past year protective jackets, made of flexible fiber-glass laminate (doron) or nylon fiber, that cover the trunk have been worn by many troops in Korea. These jackets, which weigh about 7 pounds, have significantly reduced both the incidence and the seriousness of thoracic, upper abdominal and spinal-cord wounds by screening out many of the missiles of relatively low velocity. In turn, the number and severity of casualties with wounds of the unprotected portions of the body appear to be on the increase.

Tissue Effects of High-Velocity Missiles[6-14]

A surgeon is concerned with the amount of tissue damage in a wound and the study of wound ballistics gives some answers that may aid him to determine the extent of wound revision necessary for rapid recovery and effective wound healing.

The extent of tissue injury from a low-velocity weapon is well demarcated. When a sharp instrument, such as a knife or bayonet, is forced into the body, it merely severs the tissues with which it comes in contact. The simple cutting action permits the weapon to glide between planes of tissue. The geometric extent of the damage is confined to regions actually touched by the weapon, and primary injury occurs only in structures lying directly in the wound tract.

By contrast, wounding by a high-velocity missile (bullet or fragment) is more complex. The newer technics of high-speed motion pictures (8000 frames per second) and spark photographs and roentgenograms with exposures of one-microsecond have added considerably to the knowledge of the various local phenomena of wounding by high-velocity missiles. Thus, there is now visual documentation that a high-velocity missile not only cuts the tissues with which it comes in contact but also imparts kinetic energy to them and flings them away from its path. The effect of the missile itself, therefore, is augmented, because it creates secondary missiles out of the tissues adjacent to the wound tract. These tissues are flung away from the wound tract, chiefly in a radial direction, and initially have a velocity that is an appreciable fraction of the velocity of the primary missile. The result is the momentary formation of a temporary cavity whose maximum size is determined by the energy and behavior of the missile and the elastic properties of the particular tissue. The maximum volume of the temporary cavity is many times the volume of the projectile creating it, and the maximum diameter that it achieves is many times the diameter of the projectile. The effect of the missile's passage may be described as a small explosion in the tissues. The resultant large cavity formation produces extensive damage at considerable distance from the path of the wounding agent. The damage comprises not only the destruction of tissue from stretching and tearing but also rupture of small vessels, excessive stretching of nerves and large blood vessels,

and actual fracture of bones several centimeters away. Thus, the particular characteristic of high-velocity missile wounds is disintegration of a large volume of tissue surrounding the wound tract. The greater the energy of the missile and the greater its dissipation in tissues, the greater the mass of tissue displaced and, therefore, damaged.

The same fundamental changes occur in the body cavities as in extremity injuries. The chief differences concern the size and shape of the maximum cavity, which may be confined somewhat by skin or other anatomic structures. High-speed motion pictures of a shot through the abdomen of an animal reveal the great swelling of the temporary cavity, followed by marked constriction. Wave-like movements of the abdomen then occur, followed by muscular contraction at a much later time. Segments of bowel containing gas may rupture during recession of the temporary cavity because, with the sudden release of the compressive forces, the contained gas expands at a more rapid rate than the bowel itself. A shot through the thorax reveals very little cavity formation, owing to the fact that the thorax is primarily an air-filled region.

The head presents a special problem, since the soft brain is confined in a strong and rigid cranium. The expansion of the cavity is restrained by the skull, and very high intracranial pressure may be suddenly obtained, with the result that large regions of the brain may be reduced to pulp and the cranial bones literally blown apart. On the other hand, a low-velocity shot may penetrate and cause only local damage.

Systemic Effects

The problems of deranged physiology and metabolism in wounded men can be simulated to some degree in laboratory animals. The results of knowledge obtained in animals, their translation to man and the problems to be studied in wounded men can be evaluated only in the wounded soldier at the battlefront. The practicability of research in forward areas was established by the Mediterranean Theatre Group of World War II. Accordingly, a surgical research team was organized by the Army Medical Service Graduate School and the Army Medical Research and Development Board and set up in a surgical hospital in Korea in April, 1951. It consists of permanent members, as well as consultants and specialists, both civilian and military, assigned on a temporary-duty status for the purpose of advising the team on specific problems. The mission of the team was to study the severely wounded casualty before and during resuscitation, with emphasis on problems associated with the use of whole blood, plasma and plasma substitutes, and in physiologic disturbances in the severely wounded man; during operation, with attention to abdominal hemorrhage and vascular injuries; and postoperatively, with consideration of secondary hypotension, post-traumatic anuria, wound healing and infection.

Studies in World War II[15] and now in Korea[16-18] have contributed materially to understanding of these effects, and portions of the knowledge gained from these studies are summarized below.

Subjective distress of the wounded is caused by three main factors: pain, anxiety and thirst. In the severely wounded man in good condition, the first two factors are important, although the severity of pain is not as great as one might expect. In the man in shock, thirst is the predominating complaint, and it may be extreme.

A series of metabolic and endocrine changes are set in motion by severe injury. These changes involve the autonomic nervous system, the adrenal gland, the wound itself and other factors. Defects in the adrenocortical response have not been detected. (Details will be published by members of the Surgical Research Team.)

Patients in shock show certain aberrations from the normal in terms of laboratory tests. Soon after bleeding, the hematocrit may still be normal, and then it falls as hemodilution takes place. In deep shock and in abdominal injuries, however, the hematocrit rises. The plasma nonprotein nitrogen rises strikingly after wounding. There may be significant rises in creatinine and phosphorus. Metabolic acidosis may ensue, with a fall in pH and carbon dioxide combining power and a rise in fixed acid concentration. No evidence of salt deprivation is found on hospital entry. Urinary function as measured by the excretion of phenolsulfonephthalein dye shows that in the presence of shock with hypotension the average dye excretion is low, especially during the first thirty minutes. The amount of dye excreted decreases as the severity of shock increases. Renal blood flow, as measured by para-amino hippurate clearance, is reduced in proportion to the severity of wounding for several days after injury.[33] The glomerular filtration rate, as measured by inulin clearance, is depressed to a lesser extent, except in massive wounds.

Management of the Wounded

Resuscitation of the Severely Wounded

Principles. Wounding causes local damage, which in turn leads to the profound systemic changes that are collectively referred to as shock. The seriously injured can be resuscitated only when measures to restore blood volume and other deranged physiology precede or accompany essential wound surgery for the purpose of arresting hemorrhage and revision of the damaged structures for the prevention of infection; resuscitation thus consists of the correction of shock and the performance of vital surgery. Better criteria are needed for deciding when the injured man can tolerate the added insult of anesthesia. The degree of shock in men injured in battle closely parallels the quantity of blood actually

lost and the extent of tissue damage in most cases. Conversely, resuscitation from shock usually results from the early administration of whole blood except when loss of blood is so rapid and so great that it is impossible to transfuse blood fast enough to keep up with the continuing loss. In these cases the usual cause is internal bleeding of major importance and the only recourse is to attempt its surgical control without further delay. It is apparent that the time lag from wounding to institution of effective therapy is a matter of crucial importance to the survival of many patients. The use of the helicopter in Korea has been of aid in rapidly evacuating seriously wounded patients from the battalion aid station to the army surgical hospital.

Use of sedation.[19, 20] If the pain is severe morphine, 10 mg. (1/6 gr.), is given intravenously. Patients in shock and those with head or chest wounds do not receive morphine unless pain is extraordinarily severe, because of its respiratory-depressant effects.. An important part of the discomfort endured by the wounded is contributed by the anxiety, fear and apprehension. If this component is reduced by a barbiturate, 60 to 120 mg. (1 or 2 gr.), administered intravenously, and if reassurance is rendered, the requirements for morphine are significantly reduced. Maximum comfort can be produced by the combined intravenous use of small doses of morphine (10 mg.) and a barbiturate.

Cohen and Beecher[21] have shown that, milligram for milligram, morphine, methadone and levo-isomethadone are analgesic equivalents. This is important because the methadones have the extraordinary advantage that they can be made easily from cheap and common chemicals. Thus, if sources of opium are cut off, there should be no shortage of effective pain-relieving agents.

Use of whole blood. A statement of Crosby's[16] regarding blood transfusions in battle casualties is worthy of consideration:

> The use of whole blood for resuscitation of the wounded has been fully exploited and carefully studied during the Korean War. In 1952, for example, over 60,000 transfusions were given in the hospitals supporting the U. N. Forces. Most of this blood was collected in the United States.
>
> The surgeons in the military hospitals in Korea have become increasingly bold in the use of large transfusions for the resuscitation of the severely wounded. Ten or 20 or even 30 pints of blood may be administered to a single patient within a few hours' time. Their criterion is the clinical response of the patient, rather than a tabulation of units of blood administered. Among the severely wounded some patients require more blood than others. Laceration of the colon with gross contamination of the peritoneum may produce a severe and refractory state of shock without any great loss of blood. In order to help raise the blood pressure these patients may be deliberately "overtransfused." With returning competency of the circulation such patients may develop signs of generalized congestion. They almost invariably become polycythemic and may remain so for several weeks. When wounds damage or destroy large amounts of tissue, as in bilateral traumatic amputation of the thighs, much more blood may be required. The requirement is not entirely on the basis of the severity of the initial hemorrhage. During the period immediately following the wound a very active hemolytic process is apparently at work in such patients. There is little of the conventional display of released hemoglobin or bilirubin to mark this period of intense hemolysis, but measurements of blood volume may fail by a wide margin to account for all of the blood given, and, furthermore, the patients with this sort of wound almost invariably become anemic during the first few days of convalescence. The distinction between them and the patients with severe abdominal wounds is quite evident. The surgeons have learned to use blood rather gingerly in the abdominal case in order to minimize the possibility of congestion, but they tend to be lavish where there is much tissue damage in order to avoid acute anemia.
>
> The rapid transfusion of large quantities of stored blood has not been found to produce in wounded men any untoward effects due to elevation of plasma potassium, plasma hemoglobin or hypocalcemia from citrate. It does not cause any clinically important defect in the coagulation mechanism. It does not result in a lack of leukocytes or platelets, neither of which is provided by stored blood; the bone marrow evidently keeps pace with the replacement.
>
> All of the blood sent to Korea was group O, Rh Positive. It was given without cross-matching to all patients regardless of their own blood group. The plasma of group O blood contains antibodies against A and B red cells. When small amounts of blood are given these antibodies are believed to be rapidly neutralized and therefore cause no damage to the recipient's red cells. Wounded men of groups A, B and AB who receive large transfusions of group O blood, were found, by laboratory studies, to destroy some of their own cells. This was not a clinical hemolytic reaction. It proceeded slowly over a period of several days after the transfusion. In some of these patients the foreign iso-antibodies persisted in the circulating plasma for as long as ten days. During this time it was impossible to cross-match the patient's blood with donor blood of his hereditary group. It is suspected that severe hemolytic transfusion reactions have occurred when a patient, after receiving large amounts of O blood, was subsequently given locally procured blood of his own group. It has been recommended that the switching of blood groups be avoided for at least two weeks after the universal donor transfusion.
>
> In "dangerous universal donors" the titer of antibodies is so high that it is apt to produce hemolytic reactions in susceptible recipients. Blood from dangerous donors is identified at the blood processing laboratories at Travis Air Force Base, California, and in Tokyo, and such blood is labelled to be used only for group O recipients. These individuals cannot be injured by the A and B antibodies. The typing of the blood and the identification of the dangerous universal donors is well done. During 1952, when more than 60,000 transfusions were given in Korea, only 4 patients were admitted to the renal treatment center with evidence of post-transfusion hemoglobinemia. The cause of these four reactions was not established, but it is significant that all four had been given matched fresh blood that was locally procured.

Use of plasma expanders.[17, 22] At the beginning of the Korean action the only reserve supply of adequate material (besides blood and a limited amount of serum albumin) for the treatment of shock consisted of World War II stocks of dried plasma. It was known that the proteins of these stocks were biologically suitable, but the tubing, packaging and diluent had passed a safe expiration date, and the incidence of serum hepatitis in this material, which was mostly obtained from 50-donor pools, was 5 per 100 recipients. After wide acceptance of the work on the effect of irradiation on the hepatitis virus, it was decided in 1948 to recall, reconstitute, irradiate, reprocess and reuse the plasma for stockpiling. The outbreak of hostilities in Korea occurred before this program had been completed and required the use of both the old, nonirradiated material and the new, reconstituted, irradiated plasma. In 1950 a critically controlled study of casualties from Korea returned to hospitals in the

United States[23] revealed that the incidence of serum hepatitis in those who had received plasma was about 20 per cent. Although it could not be determined accurately how much this could be attributed to the old plasma and how much to the irradiated plasma, the pattern of incidence made it appear that irradiation did not effect a virus-free preparation.

In this period intensive studies in the armed forces and in civilian agencies with plasma expanders were under way. Of these, dextran had had the most extensive testing, and limited supplies were consequently made available in Korea for use under supervision of the Surgical Research Team. Dextran has approximately the same therapeutic effectiveness as plasma in circulatory collapse. Some of its advantages are as follows: in the first place, it is cheaper than plasma; secondly, the packaged unit is ready for infusion and no time is lost as in reconstitution of plasma; thirdly, in cold weather dextran remains fluid in temperatures below that possible for the water required for the reconstitution of dried plasma; fourthly, the risk of serum hepatitis is avoided; and, finally, the incidence of untoward reactions is low. Dextran in the blood results in hemodilution, with a decrease in hematocrit, erythrocyte count and total protein concentration. For this reason it is neither a "blood nor a plasma substitute," but is rather an emergency stop-gap agent. Current experience suggests that 1500 cc. is the maximal volume to be infused safely; thereafter, blood and dextran may be used in a ratio of 1:1.

Use of antibiotics.[24] In contrast to World War II, when the armamentarium against bacterial infection consisted only of the sulfonamide drugs, and later penicillin, the antibiotics now available in Korea include streptomycin, chloramphenicol, chlortetracycline, oxytetracycline and polymyxin. Main reliance for prophylaxis against infection in war wounds is on penicillin and streptomycin. Administration of these agents against impending infection is begun on receipt of the patient in the battalion aid station. Penicillin in doses of 300,000 to 600,000 units is given initially at the battalion aid station; if the wound involves the perineal region or if the peritoneal cavity has been penetrated, 1 gm. of streptomycin is also given and these medications are repeated at twelve-hour intervals. Since the patient is frequently in circulatory collapse, the penicillin or streptomycin, or both, should be given intravenously in whatever fluid is begun on arrival at the battalion aid station, so as to provide an immediate high blood level until absorption from other routes can supply adequate bacteriostatic concentrations. As with the delayed absorption of morphine from subcutaneous tissue, experimental investigations in animals[25, 26] and in battle casualties[27] have shown that absorption of antibiotics given by the intramuscular route (particularly procaine penicillin) is delayed and irregular in hemorrhagic and traumatic shock; on the basis of these studies it is concluded that the intravenous route of administration is the only reliable means of ensuring adequate blood levels of antibiotics when circulatory collapse is present.

The broad-spectrum antibiotics are reserved for known cases of sensitization to penicillin or streptomycin, for patients in whom the oral route of therapy is desired and, in cases of invasive infection, when mixed streptomycin-penicillin therapy is of no avail or less effective than the broad-spectrum drugs. Otherwise, these agents are reserved for the occasional case of gas gangrene, for peritonitis and other severe mixed infections, and for the "medical" infections, such as bacillary or amebic dysentery. The intravenous route of administration is employed when the oral route cannot be used effectively. Polymyxin is reserved for proved infection with *Pseudomonas aeruginosa.*

It must be emphasized that antibiotics are adjunctive agents to the surgical management of traumatic wounds. The following principles have once again been demonstrated in Korea:

The key to infection in battle wounds is tissue devitalized by the contaminated missile and wound environment.

Contaminated blood clots and hematomas are comparable to masses of devitalized tissue.

Dead fascia, tendons and bone become detached from living tissue only by a slow process of sequestration, and spontaneous extrusion may, in fact, be impossible.

Precise identification of wound flora is a formidable task, and the administration of antibiotics in the management of battle casualties is therefore based on knowledge of the properties of these drugs.

The use of antibiotics in military surgery is to prevent infection after proper wound toilet or to treat already established infection originating in necrotic tissue. For this reason they are not intended to replace immediate surgery, complete excision of devitalized tissue or the surgical drainage of pus.

Use of vasoconstrictors. Available data regarding the use of vasoconstrictors in the wounded patient in Korea suggest the following points:

They should not be employed preoperatively in the patient who has a reduced blood volume.

During operation these agents, particularly norepinephrine, are specific to correct the vasodilatation due to the autonomic blockade resulting from the induction of anesthesia.

In the postoperative patient with an adequate blood volume whose blood pressure falls in the absence of further loss of blood, the administra-

tion of vasoconstrictors may be of value, although the effect is often only temporary.

Management of War Wounds of Soft Tissues[4, 28-34]

As a result of trauma, there is a variable amount of devitalized tissue in most wounds. This is minimal in wounds caused by low-velocity and maximal in those caused by high-velocity missiles. Dead and devitalized tissue in a wound does not become revascularized and incorporated in the healed wound by process of repair. The main function of the surgeon is to excise the devitalized tissues rapidly — a procedure that nature would require days or weeks to accomplish by sloughing.

Objectives of treatment. Every primary operation is in preparation for delayed closure about five days later, and for any subsequent reconstructive work that may be necessary. It has the following three main objectives in view: to remove all tissues so damaged that they are already dead, or their blood supply rendered so precarious that the wound will fall prey to infection; to open the wounds for inspection of all recesses, remove accessible foreign bodies, dirt and blood clot and control bleeding, as well as to repair, when possible, any torn or damaged major blood vessels, or to ligate them whenever repair is impossible; and to relieve local tension by incision of fascial compartments, thereby permitting decompression and escape of blood and blood clots, and at the same time designing the operation in such a way that free drainage is established (counterincisions may be required).

At the end of the operation the wound is left open because primary closure of a contaminated wound will not withstand the additional trauma of transport, and some wounds may harbor contaminated dead tissue even after presumably adequate débridement. This applies particularly to injuries from high-velocity missiles, in which differentiation of damaged and dead muscle is difficult. Leaving the wound open is the simplest possible method of providing the drain that is necessary after a battle-incurred injury, though supplemental counterincisions for dependent drainage must, of course, be employed whenever they are indicated,— for example, in wounds on the anterior aspect of the thigh. Under no circumstances is packing employed. Packs simply increase the size of the defect by forcing the tissues apart and in so doing convert it into a rigid-walled and potentially infected crater. Greases and ointments (including petrolatum-impregnated gauze) are also contraindicated; they do no good, and they may do harm because they plug the wound and thus prevent localization and allow spread of infection that may be present. Fine-mesh dry dressings to keep the wound edges separated are better.

Many of the discussions in the medicomilitary literature imply that all combat-incurred wounds must be left open at initial surgery. In soft-tissue wounds, particularly those of the extremities, this is so desirable a practice that for all practical purposes it is mandatory. On the other hand, a moment's reflection will make it clear that in many types of wounds this procedure is unnecessary, impractical, or both. These include simple wounds of the scalp; craniocerebral wounds in which the dura is reconstructed and the scalp defects are sutured in layers (to leave such a wound open would invite herniation and infection); wounds of the face, because the regional blood supply is usually excellent; wounds of the eyelids, chiefly to protect the eyes; wounds of the thorax, in which air-tight closure is essential to prevent or correct the sucking type of injury (closure is accomplished with muscle, diaphragm or lung); wounds of the abdomen, in which all layers are closed except skin, which may be loosely approximated; and wounds of the joints, in which the capsular and fascial elements, but not the skin, are closed.

In wounds of the hands and feet, a few sutures may be placed in viable avulsed skin to prevent its rolling up, but actual closure is not carried out.

(To be concluded)

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MEDICAL INTELLIGENCE

TREATMENT OF PEDICULOSIS CILIORUM IN AN INFANT

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PEDICULOSIS (infestation with *Phthirus pubis* or crab lice) involving the eyelashes and the edges of the eyelids is rare in the normal adult but less rare in the infant (Fig. 1), who is usually infested by direct passage of the lice from the axillary or chest hair (Fig. 2) of the parents or nurse or attendant. The lice are visible to the naked eye or can be seen with the help of common magnifying glasses.

FIGURE 1. *Pediculosis of the Eyelashes in a One-and-a-Half-Year-Old Girl.*

The therapeutic procedure is simple. The infant's head is held as firmly as possible with the help of assistants. In spite of batting eyelids, screams and tears, the struggle will be a brief one and will end to everybody's satisfaction. The lice are easily picked out with a pair of cilia forceps (tweezers) or trachoma forceps (not just any forceps). They are slipped out, and the ova (nits) as well. The removal of the nits is facilitated by the infant's tears. If an eyelash comes out with the nit, no harm is done, for another will grow in the same place in due time.

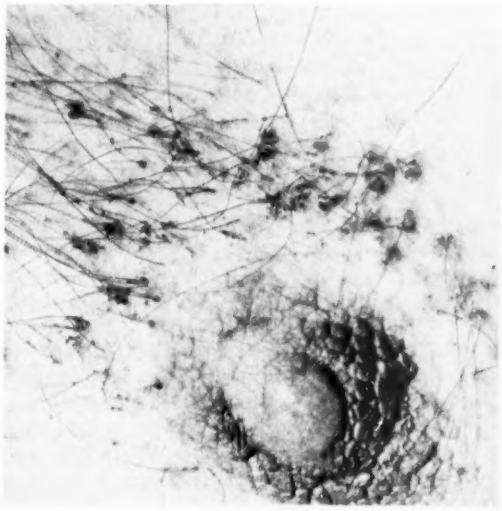

FIGURE 2. *Male Breast Infested with Nits and Lice. A male or female breast and the axillas are the most common source of infantile pediculosis of the eyelids.*

Medicaments applied before or after this procedure are superfluous. General anesthesia, which always presents a potential danger, is not recommended for such a quick procedure, especially in an infant.

In cases of such long standing that acute or chronic blepharitis has developed antiseptic or antibiotic medication may be indicated. Lice and nits are not ultramicroscopic or microscopic. If there is no blepharitis, the mechanical removal by hand is sufficient therapy. In early uncomplicated cases,

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mercury (yellow, white or blue) is not only unnecessary but also contraindicated.

The procedure is far from new. The earliest reference to manual removal of lice or nits dates back to 1886.† However, many textbooks do not mention it. Ammoniated mercury is apparently favored by most writers, many perhaps repeating statements of their predecessors without bothering to prove to themselves that there is a real need of an ointment.

The patient's lack of co-operation explains the lack of photographic documentation of this condition in the literature. One needs a great deal of patience or a movie camera. Dozens of shots and good luck permitted the selection of a fairly demonstrative case (Fig. 1), in which the infant had been infested through contact with the father's breast.‡

Out of curiosity I perused several textbooks to see what instructions are given the general practitioner for handling lice of the eyelids in an infant. The best full-page description, including manual removal by forceps, followed by a mercurial ointment, can be found in an ophthalmologic treatise. (In a way, this is reasonable: the condition affects the orbital region, and the patient is likely to seek ophthalmologic help first.)

In 3 large pediatric textbooks pediculosis of the eyelids is not mentioned at all. In a fourth the use of a mercurial ointment is advised. In a modern textbook of therapeutics there is no mention at all of the condition, and in another treatise especially intended for the general practitioner, although involvement of the eyelids is mentioned, no therapeutic hints are given.

Among assorted textbooks of dermatology, old and modern, domestic and foreign, average and good, 11 make no mention of involvement of eyelids or eyelashes, 10 advise only the use of a mercurial ointment, 22 recommend the removal by forceps, followed by a mercurial ointment, 1 suggests manual removal by the patient himself, and still another advises removal of the eyelashes. Not one advises manual removal alone, without subsequent medication. Regarding the instrument, only 1 textbook recommends removal by means of trachoma forceps; the rest merely mention forceps.

Conclusions

Recent uncomplicated cases of pediculosis pubis (crab lice) of eyelids and eyelashes in infants (and adults) are best treated by manual removal of the lice and nits with tweezers. No anesthesia is indicated. No medicament is needed after the removal. Recurrences are due exclusively to reinfestation from the same source (parents, nurse or attendant).

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†Rosenmeyer, L. Über Pediculosis palpebrarum. *München. med. Wchnschr.* 33:145, 1886.

‡Because the father's hair was very blond, no satisfactory photographs of the infested area could be taken. However, again th ough good fortune, a male patient in a mental institution offered an excellent opportunity of recording a similar infestation of the male breast (Fig. 2).

BY THE LONDON POST

The Family Doctor

John Lister, M.D.

London, England

MUCH has been said about the alteration in the character of general practice since the introduction of the National Health Service, but, until the recent publication of the report of the General Practice Review Committee,[1] set up by the British Medical Association in 1950, there was little authoritative information on the true conditions of practice.

There seem to be two major factors that have altered the character of general practice since 1948. In the first place, the ratio of insured to fee-paying patients has been altered. Before the National Health Service it was usual for most practices to have some "panel" and some private patients. The former comprised wage earners whose income bracket entitled them to participate in the insurance scheme, whereas their dependents and people with higher incomes made up the fee-paying patients. Now that so-called free medical care is available to every member of the community, it has been found that the majority of persons are availing themselves of this amenity and private patients are in the minority. Secondly, there has been an alteration in the relation between the general practitioner and the hospital. Before the Health Service many practitioners had bed privileges at their local hospitals so that patients requiring hospital treatment could often be admitted under the care of their own doctors, a visiting consultant being called upon for specialist advice, if necessary. The organization of the hospital service on a national basis, with the staffing of almost all beds by recognized consultants and specialists, has practically debarred the general practitioner from any direct control of the hospital care of a patient.

The importance of these two factors is borne out in the report and in other special articles in the same issue of the *British Medical Journal*. The 1950 Committee was asked "to review the present position in general practice, its difficulties and its trends, both generally and with reference to the two years' experience of the National Health Service Acts." The Committee approached the problem in two ways: it instructed the secretary, Dr. Stephen Hadfield, to carry out a field survey, and it conducted a postal inquiry. The report is based on Dr. Hadfield's survey of 188 personally visited practitioners and on questionnaires completed by 12,657 practitioners. The most important general impression of the report is that, despite previous gloomy accounts, most family doctors are reasonably happy in their work. Furthermore, they are doing it con-

scientiously and competently, and less downright opposition to the service was encountered than is sometimes supposed to exist.

The investigation covered a wide range of problems confronting the practitioners, but chief attention was paid to the doctor-patient relation and to that between the general practitioner and the hospital. Concerning the first point, Dr. Hadfield did not find any universal deterioration in relations between the doctor and patient, but 32 per cent of the practitioners reported a tendency to be regarded as suppliers of medicine, rather than medical advisers. At about half the consultations he attended, he witnessed the shopping-list technic, whereby a person called at the doctor's on the way home from the grocer's and asked for the drug-store requirements of two or three members of the family. Ninety per cent of the practitioners were undoubtedly interested in their patients and careful in their treatment and considered it their duty to act as "guide, philosopher and friend," in addition to being a family medical adviser. Although many doctors stated that they liked to keep a number of private patients, 43 per cent of those interviewed by Dr. Hadfield and 19 per cent of those who answered the postal inquiry stated that they did not want any private practice. These physicians asserted that their relations with patients had improved since fee charging and the rendering of accounts had become a thing of the past. On the other hand, they thought the principle of a capitation fee for each patient on the doctor's list was greatly preferable to a salary since it preserved the patient's right to a free choice of doctor — a choice that many thought would virtually disappear if all general practitioners were salaried officers.

Dr. Hadfield found that most physicians were providing adequate facilities at their offices, but 10 per cent had unsuitable premises, their rooms being bare and inhospitable. These were usually in districts where housing was inadequate and the poor conditions were often not the doctor's fault. Sometimes, it is apparently difficult to maintain a standard above that of the neighborhood, and any feature of comfort is likely to be defaced. One physician had to bolt his waiting-room chairs to the floor to prevent their being taken away, and others were discouraged by the marks of nailed boots on the floor. The daily round of visits to patients in their homes covered an average of 15 to 20 miles, and most practitioners do about 5 visits in each hour, although a few exceptionally rapid workers were met in the survey, one making 44 calls in 190 minutes.

Concerning their relations with the hospital and with their consultant and specialist colleagues, the general practitioners were critical on many points: difficulty in the disposal of the chronic sick and particularly the elderly and delay in the admission of tuberculous patients were common complaints. The increasing demand for hospital consultations has meant that a patient sent up to see a consultant is frequently seen by his deputy, who may be of junior status. Doctors also complain that increasing specialization has resulted in the allocation of beds in small batches to an ever-growing number of specialties, with fewer beds available for the general consultant, who has himself become a "rare bird."

Sir Heneage Ogilvie,[2] in a lecture to general practitioners, recognizes these difficulties and is in favor of the restoration of bed privileges to the general practitioners in certain hospitals. He recalls that the old general-practitioner or cottage hospital was under a cloud at the start of the National Health Service. This was chiefly because of the incompetent surgery that was often performed there, and such a state of affairs should never be allowed to recur. On the other hand, much good was done in cottage hospitals and Sir Heneage thinks that the medical planners tend to forget that "sick folk will get well in familiar surroundings, near their homes and cared for by doctors and nurses they know, when they would pine in the chill antiseptic surroundings of a large distant hospital subjected to the skilled but impersonal attention of strangers."

The whole of this recent review of general practice has been characterized by a frankness and sincerity that make it worthy of the most careful consideration. Emerging from it, the weakest point in the Health Service at present appears to be the gap between the general practitioners and the hospital service. In the concluding remarks of his lecture, Sir Heneage urges that the practitioner and the consultant come together. He points out that both are trained in the same basic sciences but that they have been parted by the increasing complexity of modern medicine. They have been forced further apart by some of the unexpected consequences of the new act. It is to be hoped that better co-operation will be seen in the future.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 39481

PRESENTATION OF CASE

A fifty-two-year-old clerk was transferred to this hospital because of fever of unknown origin.

The patient was well until ten weeks prior to admission when he noticed the onset of pain in the lower abdomen that persisted and was associated with cramps, nausea, vomiting and fever. Two days later physical examination was negative although he still complained of cramps and vomiting. He was admitted to another hospital, where a roentgenogram revealed small-bowel obstruction and an exploratory laparotomy was performed. The obstruction was found to be due to a mass of adhesions in the region of a ruptured appendix. The wound was drained by tube for two days, after which the tube became plugged and was therefore removed. The wound subsequently drained by itself. Penicillin and streptomycin were given. The patient did well and was discharged afebrile two weeks after the operation. Three weeks later, he was seen for a routine checkup and was found to be well. Two days later, however, fever developed, and he felt chilly and weak. He was admitted to another hospital with a temperature of 102°F. There was no abdominal pain. Physical examination and roentgenographic study of the chest were negative. The diaphragm moved freely. The white-cell count was 10,800, with 66 per cent neutrophils. The temperature gradually came down and was 99.5°F. at the time of discharge one week later. After a few days at home, chills and a temperature of 103 to 104°F. again developed. He was again hospitalized. All examinations were negative, including three blood cultures, agglutination tests for undulant fever, typhoid and paratyphoid, chest roentgenograms and intravenous pyelograms. Penicillin, streptomycin and chlortetracycline were given, but none showed any effect. Two days before admission here, he fainted. The blood hemoglobin was 60 per cent; there was no evidence of bleeding, but he was given 1000 cc. of whole blood. He continued to have intermittent chills and fever and was transferred to this hospital. He had lost 27 pounds during the illness.

Physical examination revealed a well developed, pale, chronically ill man in no distress. He appeared weak and tired. The chest was clear, and the diaphragm moved freely. The heart was not enlarged; a Grade 2 systolic murmur was present at the apex. The abdomen was soft and tympanitic. There was no tenderness, and peristalsis was normal. The liver edge was felt 2 fingerbreadths below the right costal margin and was tender on deep inspiration. The spleen was not palpable. Rectal examination was negative.

The temperature was 101°F., the pulse 120, and the respirations 18. The blood pressure was 110 systolic, 65 diastolic.

Examination of the blood disclosed a hemoglobin of 11.8 gm. per 100 cc., a white-cell count of 17,200, with 94 per cent neutrophils, a sedimentation rate of 60 mm. in one hour and a prothrombin time of 18 seconds (normal, 14 seconds). The serum sodium was 130 milliequiv., and the chloride 87 milliequiv. per liter; the total protein was 5.5 gm., with an albumin-globulin ratio of 1, and the total bilirubin 0.8 mg. per 100 cc. Brucella and Widal agglutination tests were negative, as were two stool guaiac tests. Roentgenograms of the chest, gastrointestinal series, small-bowel study and barium-enema examination were all negative. Both leaves of the diaphragm moved freely on fluoroscopic examination. Blood cultures were negative.

The patient continued to have chills and a temperature ranging between 101 and 104°F. On the fourth day, he had an episode of profuse sweating immediately after which the temperature was 96°F., the blood pressure 80 systolic, 56 diastolic, the pulse rate 60, and the respirations 20. However, he was in excellent spirits and had no complaints. The hemoglobin was 10.8 gm. per 100 cc. The hypotension lasted a few hours, and then the temperature returned to 103°F. On the sixth day, 25 cc. of Thorotrast was given intravenously for diagnosis. On the seventh day, the patient had a shaking chill lasting three hours. Three hours later, a second 25 cc. of Thorotrast was given. Films centered over the liver and spleen revealed slight opacification of these organs by the contrast substance. Four hours later, he had a drenching sweat, followed by another chill, and the temperature rose to 104°F. The next morning he had another episode of hypotension, with a blood pressure of 90 systolic, 60 diastolic. The pulse rate was 110, the respirations 44, and the temperature 97.5°F. An eosinophil count was 28 per cubic millimeter. Intravenous injections of chlortetracycline, streptomycin and Cedilanid were given. The blood pressure became unobtainable in the evening, and 10 mg. of Neo-synephrine was

administered in 500 cc. of 5 per cent glucose in water without effect; 50 mg. of cortisone was also given. The fingernails became cyanotic, and rales were heard over the lung bases. The patient died a short time later.

Differential Diagnosis

Dr. Alfred Kranes*: No mention was made of an examination of the urine. I shall assume that one was done and that it was negative.

This case, when boiled down to its essentials, consists of a patient who became febrile five weeks after an appendectomy for a ruptured appendix and who, during the period of this fever, was without symptoms or abnormal physical signs and had no laboratory findings that were at all helpful. Under these circumstances, it seems difficult to decide what he had.

In general the causes of high remittent fever of this type can be divided into three categories: the most common is the large group of infections, the second neoplasms of various types, and the third a miscellaneous group in which the collagen diseases, such as rheumatoid arthritis and polyarteritis nodosa, can be included. Although I do not think it is possible actually to exclude any of these, at least two of them seem improbable — namely, the collagen diseases, for which there was not the slightest evidence aside from the fever, and the neoplasms, although lymphoma is a possibility. I can recall several patients with lymphoma who had chills and fever for as long as five or six months before the diagnosis became evident, but it would be extraordinary for lymphoma to cause the death of a patient within five weeks and give no signs and symptoms, no x-ray findings in the chest, no splenomegaly and no lymph-node enlargement. I shall therefore confine my attention to the group of infections.

It is the nature of the infection that is puzzling. With so few leads I searched this record longingly, even desperately, for clues, and I have been able to find only four, of which two are definite and two questionable. The two definite clues are that he had an acute suppurative appendicitis ten weeks before admission and that he died of peripheral circulatory failure — shock. The two questionable findings are the systolic murmur and the slightly tender liver felt 2 fingerbreadths below the right costal margin (this was mentioned only once).

Is it actually true that this patient had no symptoms whatsoever throughout this fatal illness?

Dr. Daniel S. Ellis: He felt weak and had chills and fever; that is all.

Dr. Kranes: No aches or pains?

Dr. Ellis: That is correct.

Dr. Kranes: The most important fact is that this patient had an operation for appendicitis ten weeks before admission. How certain are we about the operative findings? In view of the subsequent course I cannot help wondering whether instead of an acute suppurative appendicitis he had any one of a number of other diseases.

Dr. Benjamin Castleman: This is the information received from the surgeon who did the appendectomy:

> I operated for small-bowel obstruction, which was found to be due to a ruptured appendix. Physical examination had previously revealed absolutely no tenderness in the abdomen, and the patient's only complaints were cramps and vomiting. At operation the small bowel was definitely obstructed in a mass of adhesions in the region of the ruptured appendix. The abdomen was drained through a stab wound in the ruptured area. He was put on penicillin and streptomycin and did very well, except that a wound abscess developed in the lower abdomen. This drained satisfactorily, and he was afebrile on discharge [about two weeks later].

Dr. Kranes: Was the appendix removed?

Dr. Castleman: That is not stated.

Dr. Ellis: That is all the information we had. Judging from the note, I assume that the appendix was not removed.

Dr. Kranes: Under these circumstances one wonders whether this patient had something other than an acute appendicitis — such as regional enteritis, with which fevers of obscure origin occur. Yet the x-ray films were normal.

Dr. John F. Gibbons: They are not revealing. The small-bowel study was negative, as were the chest films.

Dr. Kranes: Could this have been ileocecal tuberculosis, and did the operation spread the infection so that the patient had miliary tuberculosis? Or was this a perforation from typhoid fever? It seems unlikely in view of the later studies, but I cannot help wondering about it. Did he have amebiasis, with a perforation around the cecum? There is no mention in the record that the site of perforation was recognized: it said a ruptured appendix.

Dr. Castleman: That is all.

Dr. Kranes: It is conceivable that he had amebiasis and that an amebic abscess of the liver later developed. I do not know how to settle any of these questions since there is not enough evidence. All I can do is mention these possibilities. I think I shall have to accept the diagnosis of a ruptured appendix and ask myself what septic complication produced the fever and death. He may have had a pelvic, perirenal, subhepatic or subphrenic abscess, or a pylephlebitis. The only clue to the location of the sepsis is the fact that the liver edge was felt 2 fingerbreadths below the right costal margin and was slightly tender. That is not a reliable clue because many people have livers felt 2 fingerbreadths below the costal margin and will wince a bit when the liver edge is flicked under the examining hand; but it is the only clue I have. If the fever was related to the appendicitis, I should choose pylephlebitis as the most likely cause since it is the only one of the complications mentioned that is capable of causing a patient's death in so short a period. Unfortunately, there are several objections to it. Most patients

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with pylephlebitis are jaundiced. This patient's bilirubin was 0.8 mg. per 100 cc., only slightly above the upper limits of normal and hardly to be considered as constituting jaundice. Furthermore, the right leaf of the diaphragm should have been elevated, and there should have been some fluid in the right pleural cavity. To be sure, the elevation of the diaphragm will depend on the location of any abscesses of the liver. With those in the upper part of the right lobe of the liver the diaphragm is much more likely to be elevated than with those deeply embedded in the substance of the liver. Pylephlebitis may be present without liver abscess, but I should not expect that to be true in this case.

I must also explore the possibility that the chills and fever were unrelated to the ruptured appendix. Another disease may have developed, but if it did, I do not see any way of determining its nature. I see no point in listing all the infectious diseases capable of producing fever and chills, such as amebiasis and miliary tuberculosis, since I have no way of ruling them in or out. If he had any of these, I do not know how to establish the diagnosis.

Two points deserve more than passing mention. Does the systolic murmur mean that he had an acute bacterial endocarditis? I should dislike making a diagnosis of bacterial endocarditis merely on the basis of a systolic murmur. There was no other evidence of endocarditis, such as emboli, petechiae or splenomegaly. I should have expected a positive blood culture although organisms are sometimes difficult to grow.

The other point is the death in acute circulatory failure. This may occur in a wide variety of severe fulminating infections, but the most probable one is meningococcemia, the so-called Waterhouse–Friderichsen syndrome. This term is a confusing one since by some it is considered a pathological entity and by others a clinical syndrome. As it was first described by Waterhouse and later by Friderichsen, the patients died after a short febrile illness in shock, and autopsy disclosed bilateral hemorrhages of the adrenal glands. It was not until some years later that most of the patients were discovered to have meningococcemia. Subsequently, during epidemics of meningitis, it was found that not all patients dying in this fashion had bilateral adrenal hemorrhages although histologic changes were described in the adrenal glands. I am reluctant to base a diagnosis of meningococcemia solely on the way a patient dies. There is no other supporting evidence, and there seems to be a great deal against it. Most people with meningococcemia have symptoms. They complain of joint pains and usually have a rash, which may be of various types. The rash, however, may be quite ephemeral and may escape detection. Since this patient was under observation for five weeks, I should expect a rash to have been seen. Moreover, the organism is readily grown, and there should be no difficulty in finding it in the blood culture. Finally, it is quite sensitive to penicillin and chlortetracycline, which should have cured him.

Before I go back to my seat I am expected to make a diagnosis. I have nothing to go on but probability. When a fever develops several weeks after a rupture of the appendix it is most probably due to some septic complication of the appendicitis unless there is evidence to the contrary. Of these septic complications, the one most likely to produce death in so short a time is pylephlebitis. If this should turn out to be what this patient had, a possible explanation for the manner of death would be the rupture of a liver abscess, a not uncommon occurrence in this disease.

Dr. Jacob Lerman: What about the Thorotrast?

Dr. Kranes: Those who were taking care of the patient were apparently trying to visualize a liver abscess.

Dr. Castleman: Do you think the Thorotrast had anything to do with the circulatory collapse?

Dr. Kranes: I have no idea.

Dr. Reed Harwood: I should like to ask Dr. Kranes if he thinks the failure to grow out positive blood cultures is best explained by an inhibition of the bacteria by the antibiotics or by the possibility that the organisms cannot be grown from the blood.

Dr. Kranes: Either is possible. The record does not say whether he had any antibiotics in this hospital, except terminally.

Dr. Ellis: Dr. McKittrick and I decided that this patient had had almost every known antibiotic and had not benefited in any way; since we believed that further antibiotic therapy would obscure the picture rather than help him we stopped antibiotics at the time of admission. He received no further antibiotics until the last twelve hours of life; then it was a matter of desperation.

Dr. Arthur S. Pier, Jr.: Do you think the three-week period free of symptoms is somewhat against pylephlebitis?

Dr. Kranes: No; I do not. Although it is true that pylephlebitis is more likely to start while the patient is convalescing in the hospital, the delay here may have been due to the antibiotics that he received while he was recuperating. Even in the days before antibiotic therapy did not the pylephlebitis occur weeks and occasionally months after an acute appendicitis?

Dr. Leland S. McKittrick: I cannot answer that question. I think that in most cases I have seen there was not that lag period.

Dr. Castleman: I believe cases have been reported as long as three months after appendectomy.

Dr. Allen G. Brailey: Has not the so-called Waterhouse–Friderichsen syndrome been reported when organisms other than the meningococcus were present?

DR. KRANES: Yes; it is not confined to the meningococcus, but that is the most common one. Streptococci and others will do the same thing.

DR. CASTLEMAN: Dr. McKittrick, will you tell us the reasoning on the ward.

DR. MCKITTRICK: Our reasoning was much the same as Dr. Kranes'. I saw this patient with Dr. Ellis shortly after admission, and it seemed to both of us that the only logical explanation was some complication of a previous appendicitis. Since I knew the surgeon who took out the appendix, I thought I could believe him when he said it was acute appendicitis. That brought up the question, What complication was present? The first time I saw the patient I went over him quite carefully and could not find anything abnormal in the abdomen; therefore, I believed that this was not a subdiaphragmatic abscess or a pelvic abscess. Moreover the x-ray films definitely excluded a subdiaphragmatic abscess. That brought up the liver as the next possible site. My impression was somewhat different from Dr. Kranes'. For several reasons I thought the patient probably had a solitary abscess in the liver — that is, one or perhaps two abscesses, in contradistinction to pylephlebitis. The history seemed to be very suggestive. He had apparently recovered from appendicitis; then after a lag period he had a chill and symptomless fever. As a matter of fact, in some cases at least, the appendicitis has spontaneously subsided without a suspicion of the diagnosis, the complete picture being recognized at autopsy. He did not have the recurring chills and fever, — he had two or three chills during the whole course of his disease, — and he did not have jaundice, all of which I thought were against pylephlebitis.

I considered the most likely diagnosis to be a solitary abscess of the liver. We intentionally omitted the antibiotics so that the disease would have an opportunity to manifest itself. I was not too concerned about the possibility of sudden death because in my experience death has not occurred so rapidly. We brought up the question of an exploratory laparotomy, but it is difficult or impossible to find the abscess unless one is fortunate and happens to hit on it. As time went on I became convinced of the diagnosis, and I kept watching him to determine the exact location of the abscess. Finally, some tenderness developed in, I think, about the fifth right intercostal space. If I had had to operate, I should have chosen that spot. We had given him the Thorotrast in an effort either to disprove the diagnosis or to locate the abscess and thus to be able to make a direct approach to it. I criticize myself severely because I did not do all I could do to press for Thorotrast early after admission to the hospital. Once I became reasonably convinced that he had a liver abscess I should have insisted on using Thorotrast in an effort to locate the abscess or disprove the diagnosis. Whatever the hazards of Thorotrast are, they are theoretical at the moment and are not half so dangerous as the disease.

DR. WALTER BAUER: How many days before death was the Thorotrast used?

DR. ELLIS: The first dose of Thorotrast was given two and a half days before he died, the day that Dr. McKittrick felt the tenderness.

DR. MCKITTRICK: The tenderness was localized. I was quite sure that he had some infection underneath the chest wall of that area.

DR. ELLIS: I might make clear the sequence of events. In using Thorotrast in the study of the liver for abscesses, one usually gives 25 cc., takes a film twenty-four hours later, gives a second dose after that and takes a second film forty-eight hours after the first dose. If by that time the density is not sufficient to demonstrate disease in the liver, one may give a third dose. This man had a film twenty-four hours after the first dose of Thorotrast and was given the second dose, but by the time the forty-eight-hour film could be taken he was moribund and could not be moved to the x-ray department. He died twelve hours later.

CLINICAL DIAGNOSES

? Liver abscess.
Appendiceal abscess.
Pulmonary congestion.

DR. ALFRED KRANES' DIAGNOSIS

Pylephlebitis, with abscesses of liver, secondary to acute suppurative appendicitis.

ANATOMICAL DIAGNOSIS

Pylephlebitis, with abscesses of liver (secondary to acute suppurative appendicitis).

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: The autopsy showed two large abscesses in the right lobe of the liver. The larger, measuring about 15 cm. in diameter, was in the superior portion and almost reached the dome; the smaller, measuring 9 by 4 by 5 cm., was in the posteroinferior part of the lobe and communicated superiorly with the larger abscess. This smaller abscess presented on the posteroinferior surface and had ruptured to produce an abscess 6 by 3 by 3 cm. located between the hepatic flexure of the colon and the anterior surface of the right kidney. The rest of the liver on gross examination was very soft, necrotic and obviously the site of infection. The appendix had been removed. The ileocolic and portal veins looked fairly normal; we found no thrombosis as a possible source of the liver abscesses. On microscopical examination of the liver in addition to the obvious abscesses observed grossly, there was a fairly extensive polymorphonuclear infiltration throughout the liver. Many of the intrahepatic portal-vein radicles were obliterated by old organized recanalized thrombi, but there was no recent

thrombosis, indicating that the more widely spread pylephlebitis had healed by the time of autopsy about two months after the appendectomy (Fig. 1). Cultures of abscesses showed a pure growth of nonhemolytic streptococcus. Apparently, the organisms were carried through the portal circulation and, as may happen in pylephlebitis, tangible evidence in larger veins may be lacking at post-mortem

FIGURE 1. *Photomicrograph of a Portal Area, Showing an Organized Recanalized Thrombus in the Portal Vein. Note the normal hepatic artery and bile duct on the right.*

examination. I think the shock can be explained by the rupture of the smaller abscess.

DR. ELLIS: Did I understand you to say that there was an abscess in the abdominal cavity?

DR. CASTLEMAN: Yes; it was beneath the liver. There was no peritonitis; the abscess was localized in this region.

DR. GIBBONS: It is unusual to see enough opacification of the liver and spleen after the first dose of Thorotrast. Here there is a faint outline of the edges of the liver and spleen, but the opacification is not sufficient to give any contrast. We were unable to get a film after the second dose of Thorotrast because the patient died. Although an attempt was made to take a post-mortem film, there were too many technical difficulties; however, a film of the liver removed at autopsy showed a large irregular abscess cavity contiguous with a smaller one below. I am sure if we had been able to get a film before death we should have seen this distinctly in situ.

Many people are afraid of using Thorotrast because of its long-term radioactivity; it is harbored in the liver and spleen for life after it has been given. Nevertheless, in particular cases, it should be used in an effort to find trouble that something can be done about. This method is also used sometimes to find large foci of metastatic disease in the liver. Almost always it takes two doses and sometimes three to opacify the structures enough for diagnosis.

DR. PIER: Was not the liver so diffusely involved that, even if the abscesses could have been drained, survival would have been unlikely?

DR. CASTLEMAN: Yes; there was extensive disease of the liver.

DR. GIBBONS: Theoretically, if the Thorotrast had been used a month or so earlier the patient could have been helped.

DR. CASTLEMAN: We do not know how extensive the disease was at that time. He had the first operation two and a half months before death.

CASE 39482

PRESENTATION OF CASE

A forty-two-year-old chauffeur was admitted to the hospital because of abdominal cramps and vomiting.

At intervals of four to six months during the three years before admission the patient had had about six of these attacks, which were similar in onset and character, usually lasted all night and were gone by morning. He had found that he could stop them by taking enemas soon after the onset. The pain was never sharp or localized, but was colicky and did not radiate. He had never had jaundice, hematemesis, diarrhea or other change in bowel habit, and had never noted tarry or bloody stools. During the past year a Graham test, gastrointestinal series and barium-enema examination were reported as negative. The patient dated the onset of his attacks to a year or so after he "felt something give" in his abdomen while raising himself from a squatting position. He had never had any previous abdominal surgery and up to three years before admission had never had any gastrointestinal complaints. In the late afternoon, four hours before admission, he noticed the gradual onset of a sensation of abdominal distention and desire to belch. This rapidly progressed to nausea and to cramps in the lower abdomen and finally to vomiting of bile-stained material. An hour later his physician found no localized tenderness or spasm and a hyperactive, high-pitched peristalsis. The vomitus had the appearance of small-bowel contents. The cramps and vomiting continued, and the patient was referred to the hospital. At that time he had his fifth bout of vomiting since the onset of the attack, and was bringing up brown, watery material that had a strong fecal odor.

Physical examination revealed a well developed and well nourished man who was sweating and pale, and appeared acutely ill. The heart and lungs were normal. In the abdomen, peristalsis was visible, with hyperactive sounds. There was no tenderness or spasm; no masses or enlarged organs were palpable.

The temperature was 97.8°F., the pulse 92, and the respirations 24. The blood pressure was 130 systolic, 82 diastolic.

Laboratory studies on admission included a urinalysis, which showed a specific gravity of 1.012, a ++ test for albumin and an olive-green sugar reaction. The sediment contained 6 red cells, 5 white cells and occasional hyaline casts per high-power field. The white-cell count was 19,000. A plain film of the abdomen revealed several dilated loops of small bowel, with fluid levels primarily restricted to the left upper quadrant. There was little if any gas in the colon.

A Miller–Abbott tube was passed, but despite this the patient vomited 600 cc. of brown, watery material during the night. He had no further pain. On the following morning the temperature was 101.2°F., but there was no tenderness anywhere on abdominal or rectal examination. Peristalsis was very inactive, and no high-pitched sounds were heard. The abdomen seemed "full." The patient had not passed gas by rectum. The hemoglobin was 14.2 gm. per 100 cc., and the white-cell count 9100, with 78 per cent neutrophils, 12 per cent lymphocytes and 10 per cent monocytes. A stool specimen was brown and guaiac negative. The serum sodium was 139 milliequiv., the chloride 101 milliequiv., the potassium 4.2 milliequiv., and the carbon dioxide 23 milliequiv. per liter. The prothrombin time was 16 seconds (normal, 14 seconds). A second plain film of the abdomen showed findings much as before. Later the same day an operation was performed.

Differential Diagnosis

Dr. William V. McDermott, Jr.*: This picture, as I visualize it from the protocol, is obviously one of intestinal obstruction; I think it is fair to say that it is a classic story of acute small-bowel obstruction, since within four hours of admission the whole syndrome rapidly developed to a point where the patient was distended, had spasm and high-pitched peristalsis, and was vomiting continuously. Before I dig too deep a beartrap, perhaps I had better see the x-ray films.

Dr. Stanley M. Wyman: These two sets of films were taken on successive days, as reported. The first set shows several distended loops of small bowel containing both fluid and air in the left upper and middle portions of the abdomen. There is very little, if any, gas in the colon. The next set demonstrates the same findings; there is a definite loop in the left upper quadrant, and two loops seem to have remained remarkably constant in configuration and degree of distention, suggesting that they are perhaps held by some mechanism.

Dr. McDermott: The dilated loops of small bowel are not confined to the left upper quadrant.

Dr. Wyman: That is true; one comes down in the right center, and one in the left lower abdomen.

Dr. McDermott: There is no gas in the large bowel that I can see. Were the other films normal?

Dr. Wyman: They do not show anything conclusive.

Dr. McDermott: The plain films are typical of acute small-bowel obstruction and thus confirm the impression given by the history and clinical findings. Possibly, from the history, there was early strangulation, although it is difficult to determine that; the time between the onset of obstruction and the operation was short and probably not long enough for actual strangulation obstruction to develop to the point where gangrene was imminent. One statement in the history that might be mentioned is that the cramps were located in the lower abdomen. Ordinarily, that would be disturbing, for we refer to the cramp associated with small-bowel obstruction as occurring in the upper abdomen or at least in the periumbilical region; however, the known vagaries of a history obtained from a sick patient are such that it does not deter me too much. I should not consider large-bowel obstruction on the basis of the information given here despite the location of abdominal cramps noted in the history. The patient had a bowel movement after admission, but the colon frequently empties itself after the small bowel has become acutely obstructed.

If I accept the diagnosis of acute small-bowel obstruction, I must attempt to explain the possible causes, the most common of which is an external hernia. I can assume, since it was not mentioned positively, that no external hernias were palpated; therefore, I can rule out that possibility. Statistically, the next commonest cause of intestinal obstruction is postoperative adhesions either early or late. Since the patient had had no prior abdominal operation, I can also rule out that possibility.

By eliminating those two possible explanations I limit myself to the causes of about 10 per cent of all small-bowel obstructions. Actually, from the information available, I probably shall not be able to tell definitely the cause of the intestinal obstruction; nevertheless I can run over the possible causes that fall in this 10 per cent group to see if by inference and deduction I can arrive at a likely diagnosis. I should like to discuss them in ascending order of probability. Among these is the interesting syndrome of agnogenic, mesenteric, venous thrombosis. Although it may occur in young men and may mimic the picture of small-bowel obstruction, it is ordinarily associated with remarkably rapid onset of severe pain; this man really had no abdom-

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inal pain or tenderness. Moreover, with this syndrome there is usually a rising white-cell count, prodromal symptoms of previous clotting episodes, migratory phlebitis and so on. I think this explanation is unlikely.

Gallstone ileus, another possibility, is a relatively frequent cause of intestinal obstruction in this particularly uncommon group to which I have limited myself. Gallstone ileus is rare in young men, and the Graham test taken in the year before entry was reported to be negative. The obstruction with gallstone ileus is usually chronic and not acute and complete as it apparently was in this man. There was no air in the biliary tree that I could see in the plain film; although air is not invariably found, it is often associated with a gallstone ileus as a result of a cholecystoduodenal fistula, which is the port of entry for the gallstone.

The third possibility is intussusception. In the series reported from this hospital[1] about 25 per cent of the cases occurred in adults, in whom it is usually not idiopathic as in infants. The intussusception in adults is generally associated with a small-bowel tumor or a Meckel diverticulum. One would expect that a palpable mass would have been found, particularly since the patient had no abdominal tenderness or guarding. In addition, he had a bowel movement some hours after admission, and the stool was guaiac negative, so I should consider all these facts very much against the diagnosis of adult intussusception.

The fourth possibility is adhesive band on some basis other than prior operation, either congenital or postinflammatory in origin. Nothing in this man's history suggested a prior inflammatory condition within the abdomen. His previous attacks during the three years before admission were quite similar to the presenting syndrome of acute small-bowel obstruction and in all probability were attacks of small-bowel obstruction, whatever the cause, which spontaneously reduced. Congenital adhesive bands do exist, but I shall discuss this condition more fully in a group of possibilities that I consider more likely. I think I can pass over the possibility of torsion of the omentum fairly rapidly. This syndrome, which recurrently, though rarely, appears on any surgical service, to my knowledge from the reports in the literature, has never been diagnosed preoperatively. Ordinarily, the mistaken diagnosis is that of some acute inflammatory condition within the abdomen, frequently appendicitis. The findings are almost invariably those of localized tenderness and abdominal spasm, none of which this man presented.

I am left with three possibilities to consider at greater length — internal hernias, volvulus of the small bowel and an anomaly associated with a persistent omphalomesenteric duct or artery. Among the internal hernias, I should like to discuss first the diaphragmatic hernias, which can cause small-bowel obstruction; the foramen that is the most common site of herniation, although all these possibilities are rare, is the pleural peritoneal hiatus. There is an occasional small-bowel obstruction associated with herniation into the pleural peritoneal hiatus, but that is almost invariably associated with signs and symptoms referable to the chest and some cyanosis and dyspnea, which did not appear here. The foramen of Winslow is another esoteric site of possible internal herniation or invagination of small bowel, with resulting obstruction. Characteristically, however, this obstruction develops slowly, ordinarily is not acute in onset and is rarely complete until a considerable time has passed. The paraduodenal hernias certainly present a distinct possibility in this case. Lord Moynihan[2] described at least nine different fossae into which herniation with the development of small-bowel obstruction could occur, but I think we can group them into those of the right and those of the left paraduodenal areas. That possibility I do not think I can rule out definitely, but in the plain films of the abdomen in these cases the intestines usually appear to be enclosed in a bag and lie in either the right or the left upper quadrant, depending on which of the major fossae are involved. The dilated loops of small bowel in these films are scattered throughout the abdomen and do not seem to be incarcerated within the enclosed sac. These paraduodenal hernias are frequently associated with a long history of varied prodromal symptoms none of which this man had, since I am considering that these previous episodes of short duration probably represented prior attacks of acute transient small-bowel obstruction.

Volvulus of the small bowel from a congenital defect in the fixation of the mesentery is a possibility. Torsion of the small bowel on an elongated and inadequately fixed small-bowel mesentery can occur and can be the cause of sudden complete

small-bowel obstruction. I cannot rule out this possibility although it is rare.

The third and last of this group consists of the anomalies of the yolk stalk: the omphalomesenteric duct and the omphalomesenteric vessels. In the process of development there is often incomplete occlusion of these structures, more commonly incomplete disappearance of the right omphalomesenteric artery, forming a fibrous band attached to the small-bowel mesentery, or incomplete disappearance of the omphalomesenteric duct, the so-called Meckel diverticulum, with an open communication with the umbilicus or with a band attaching the pouch to the umbilicus. These anomalies may be associated with episodes of small-bowel obstruction, even with complete obstruction such as this man presented.

I do not know on what basis I could accurately select the cause of this patient's small-bowel obstruction. He needed to be operated on after he had been deflated and rehydrated; the source of the obstruction, whatever it was, would be dealt with at that time. Consideration of these esoteric possibilities, therefore, may be somewhat academic from the surgeon's point of view, but it does bring up interesting discussion of the causes of small-bowel obstruction in the absence of prior operation and external herniation. If I have to select, I shall have to use statistics as the basis of selection. From these three possibilities — internal hernia, volvulus and congenital anomalies around the omphalomesenteric duct — I should probably select a persistent omphalomesenteric artery or band from a Meckel diverticulum — in other words, small bowel that twisted around a fixed point in the region of a Meckel diverticulum and became acutely obstructed.

Dr. Winfield S. Morgan: Dr. Ellis, you are the physician mentioned in the protocol; would you like to tell us your opinion?

Dr. Daniel S. Ellis: It was obvious on admission that the patient had intestinal obstruction because the vomitus was fecal, which it had not been when I saw him two hours before admission. The fecal vomitus, with the findings in the x-ray films, made me believe that he had a high intestinal obstruction and that the three possibilities that Dr. McDermott considered seemed to be the ones entertained although I do not think we decided verbally on one of them before operation. At the time I admitted the patient I did not refer to my office record. I read my office record this morning and found that I first saw him about three years before admission, when he had a two-year history of intermittent attacks. I might quote the record: "this sounds more like abdominal migraine to me than anything I have heard in a long time since all his previous studies — he had been studied thoroughly — have been negative. I do not believe he has any ulcer, gallstones or neoplasm but he might have a Meckel diverticulum." I followed him and saw him again six months later, when I made the remark that, "the nature of his disease is still not clear, I have not seen him in an acute attack; this must be done before the diagnosis can be made, but I continue to think that he may have a Meckel diverticulum or intussusception."

Clinical Diagnosis

Small-bowel obstruction.

Dr. William V. McDermott, Jr.'s Diagnosis

Persistent omphalomesenteric artery or Meckel's diverticulum, with acute small-bowel obstruction.

Anatomical Diagnosis

Meckel's diverticulum, with acute small-bowel obstruction.

Pathological Discussion

Dr. Morgan: Dr. Donaldson, will you describe the surgical findings?

Dr. Gordon A. Donaldson: I think Dr. McDermott gave an excellent discussion of this case. I, too, was struck with the fecal type of vomitus that this patient had within four hours of the onset of symptoms, and this made me believe that he ought to be explored. The anesthetist is usually very insistent about obtaining a diagnosis before an operation. In this case he was lenient, because he accepted the diagnosis of small-bowel obstruction. We had thought that this patient probably had an internal adhesion, perhaps secondary to appendicitis, as one of the original episodes of pain described in the protocol. I thought of an internal hernia as a second possibility.

At operation the small bowel was moderately distended except for the terminal ileum, which was collapsed. The lower bowel was picked up and followed in a cephalad direction. At this point something kept nudging my elbow, and Dr. D. J. Glotzer, who was across the table, reached over, grasped a

long, tubular structure that looked somewhat like a small automobile tire and pulled it out of the abdomen. It proved to be a huge Meckel diverticulum, such as I have never seen before. This distal, bulbous end was firm and rather fibrous, and there was a neck, where it was constricted. The tip was nonadherent, and the large sac lay free to swing about as a pendulum. The weighted end had produced a

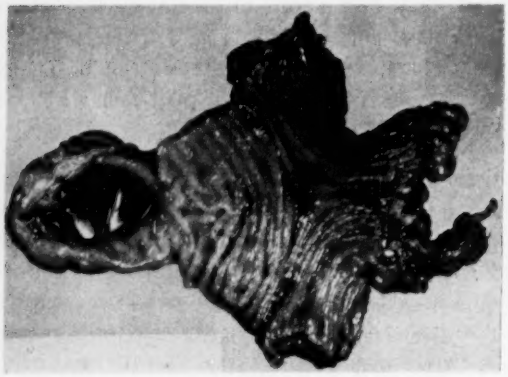

FIGURE 1.

torque in the bowel, which was obstructed for that reason. Actually, the obstruction was incomplete.

DR. MORGAN: The specimen that we received in the laboratory was a 6-cm. segment of small bowel and the diverticulum, considerably shrunken down. The most striking finding was the presence of several black, smooth-surfaced stones, which looked more like gallstones than fecaliths (Fig. 1). In our experience these have been very rare findings in a Meckel diverticulum, and the reason why they develop in some diverticula and not others is not clear. Microscopical sections of the diverticulum showed that it was lined by gastric mucosa, without ulceration, and that there were Brunner's glands and pancreatic tissue in the wall. A few years ago Allen and Donaldson[3] reported a similar case; perhaps Dr. Donaldson will tell us about it.

DR. DONALDSON: In that case the Meckel diverticulum was discovered incidentally in the course of a right colectomy for cancer of the colon. The patient had had a cholecystectomy for stones twelve years before. Stones were found in the diverticulum at the time of the right colectomy. Ten previous cases are reported in the literature. The general belief is that these stones are primary in the Meckel diverticulum as a result of changes therein, and are not gallstones.

DR. MCDERMOTT: These were not gallstones?

DR. DONALDSON: I believe they were not; one is being analyzed.

DR. MCDERMOTT: I was wondering if I had treated that Graham test too casually.

DR. MORGAN: In none of the previously reported cases were the stones found to be radiopaque. In 1 case they were analyzed and were said to consist of fecal material and bile pigment. In view of this it would probably be better to call them fecaliths although they certainly are distinctly different in appearance from those commonly found in the appendix.

ADDENDUM

DR. MORGAN: Chemical analysis of one of the calculi in the diverticulum showed that there was approximately 50 per cent ash, with no phosphorus or magnesium but +++ calcium, ++++ cholesterol and + bilirubin. This report suggested that they were gallstones. Although this development still leaves us uncertain about the site of origin of the calculi, I am inclined to believe that they developed in the Meckel diverticulum.

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ONWARD THY DESTINIES

THE *Journal*, as an instrument that has played some part in the medical flowering of New England, cannot escape a feeling of consanguinity with all the other institutions that have contributed to the culture and the intellectual prosperity of this sometimes physically reluctant area. If for this reason alone it is interested in the inauguration, by the university sheltering the oldest of New England's six medical schools, of its twenty-fourth president in the 318th year since its founding.

The importance of such an event at Harvard and the part that Harvard's president plays in guiding the destinies of the University is illustrated by the familiar story of President Eliot's first meeting with the faculty at the Medical School. A professor, conscious of certain violations of academic tradition, demanded an explanation. "It is easy to explain," said Mr. Eliot; "Harvard has a new president."

The long tenures of office that have been responsible for the University's having had but three presidents in eighty-four years make the advent of a new administrator seem something like the ending of an epoch and the beginning of another. In view of such long tenures the duty of every new president of any university is to inaugurate change; to set the vessel on another tack — the last having presumably fulfilled its forward function — and trim the sails afresh.

Each of Harvard's last three presidents has advanced learning at the University according to his own gifts; each has happily given the institution the fresh impetus and the changed bearings that it seemed to need at the time. Eliot, the chemist, by liberalizing the curriculum, developing the graduate schools, and attracting topflight scholars, turned a somewhat provincial aggregation of faculties into the greatest seat of learning in the Western Hemisphere; Lowell, the professor of government, created the physical plant necessary for Harvard's increased activities, even while maintaining the integrity of its academic tradition; Conant, another chemist, modernized the curriculum and raised still higher the standards of scholarship and research.

Pusey, trained in the liberal arts, an inspired and inspiring teacher, has indicated a fresh course for the University with a new emphasis on its practical relations with the world at large. This emphasis will apparently be on serviceable rather than pure scholarship; it will be on the broad, "holistic" aspect of education rather than on a too exclusive preoccupation with its depth; it will give a greater recognition to the spiritual values that science has been unable to replace.

Already, in placing reliance on faith above President Eliot's reliance on knowledge, the new president has given his blessing to a revitalized Divinity School. The first president to participate in an exercise of the School since 1909, he has established its scholastic location as "not on the periphery of Harvard University" and "not remote from any region where the serious business of men is done — and it cannot be permitted to become so." For, as

he said at the Convocation on September 30, "if the trumpet give an uncertain sound, who shall prepare himself for the battle?"

That there must be a shift from too great a concern with the research laboratory and the cloistered study to the classroom is implied in his statement that the major task at Harvard "remains the education of youth and advancement of learning." The main objective of the University is still to see that "young people must become dissatisfied with the culture they accept and this is why it is necessary first to start revolutions in their minds and spirits."

In the recognition of these moral and spiritual values and of the obligation to train young people for service one may find an admission that science has become the too ready tool of destructive forces; that concentration of intellect and depth of learning have not been able to avert many of the catastrophes with which human relations abound. Harvard needs now — and, it seems, has discovered — a leader to integrate the various disciplines in which useful educational experiences may be found — one who will start revolutions in the minds and spirits of young people. For he is one who has met Chaucer's sublime requirements of the perfect educator — to gladly learn and gladly teach. The University may even more confidently be charged with the enjoinder contained in its Jubilee song: "Be thy destinies onward and bright!"

MELANIN

The process of producing melanin has been a mystery for many years. Numerous theories have been presented, and an enzyme hypothesis for human melanin formation was postulated over fifty years ago. It was not until 1950, however, that the enzyme, tyrosinase, which could oxidize tyrosine to melanin, was demonstrated in human pigment cells. Tyrosinase was identified in 1895 in certain varieties of mushrooms, with the demonstration of "dopa" oxidase in human skin in 1917. In the next decade some of the chemical steps in the conversion of tyrosine to melanin were worked out by Bloch and his collaborators.

Much work has been done in the last ten years since the rediscovery of tyrosinase activity in mammalian melanomas, and especially in the last four years since it has been shown conclusively that extracts from human, mouse and horse melanomas contain tyrosinase, culminating finally in the demonstration of tyrosinase in human skin in 1950.

A recent review of the subject discusses the biochemical basis of normal pigmentation and selected pigmentary disturbances in man,* explaining these disturbances on the basis of altered biochemical factors affecting melanin formation within the melanocyte. It has further been shown that certain dendritic-shaped pigmented cells in the skin are the only cells in which tyrosinase activity can be demonstrated histochemically. These cells, which have been called melanocytes, apparently arise from the neural crest in the embryo and migrate to the epidermis and to the eye. The location of melanocytes in the dermis probably represents arrested migration of the melanoblast in its course from the neural crest. The term melanoblast applies to the immature melanin-forming cell in the crest or in the course of migration or in malignant melanomas.

The process of melanin formation, as has been indicated, involves the conversion by tyrosinase of the colorless, naturally occurring amino acid, tyrosine, to an insoluble brown substance. Tyrosinase in human epidermis also requires copper for its activity since the tyrosine-tyrosinase reaction in human pigment cells is inhibited by agents that combine with copper. This reaction is regulated by various chemical and physical factors common to many enzymatic reactions, such as temperature and electrolyte concentration. However, there is some means of inhibiting this tyrosine-tyrosinase reaction in the mammalian melanocyte, for if this reaction were not inhibited melanin formation would proceed at a rapid rate and all human skin would be black.

It seems that a number of inhibitors of the tyrosine-tyrosinase reaction that block the series of reactions have been developed. Inhibition of human melanin formation is noted after the ingestion of three organic sulfur-containing compounds; thiouracil, BAL and cysteine. Ascorbic acid as a reducing agent has also been found to reduce melanin pigmentation in man. At present the monobenzyl ether of

*Fitzpatrick, T. B., and Lerner, A. B. Unpublished data.

hydroquinone is the most effective clinical inhibitor of melanin formation. It seems reasonable that the net content of melanin in the melanocyte depends on a balance of melanin formation and melanin excretion from the pigment cell, but little is known regarding the mechanism of melanin excretion, though two routes have been described — one through the dermis via the lymphatics to the lymph nodes and into the venous circulation and ultimately into the urine, and the other through the epidermis, the melanin granules leaving the melanocyte at the stratum granulosum and progressing to the stratum corneum. In the Negro skin the application of monobenzyl ether of hydroquinone often produces complete depigmentation, which is thought to be due to a more rapid excretion rate of melanin in the melanocyte in Negro skin.

Numerous factors controlling melanin formation have been worked out and will vary greatly in different persons, depending in large part on genetic factors. There is definite evidence of control of pigmentation in increased activity of the pituitary glands and of the adrenal glands as in Addison's disease, pregnancy and so forth. There are numerous reports of hyperpigmentation after the treatment of various diseases with ACTH preparations, which are known to contain the melanocyte-stimulating hormone.

This melanocyte-stimulating hormone (MSH) has been found in the urine of pregnant women and in the extracts of human pituitary glands. The administration of pituitary fractions containing a high concentration of MSH has been associated with a rise in serum copper. This is of interest in view of the fact that elevated serum copper and increased urinary MSH occur in pregnancy, Addison's disease and starvation melanosis. The term melasma has been proposed to designate the triad of hyperpigmentation, elevated serum copper and increased urinary MSH. MSH appears to affect melanin formation in human beings.

Phenylalamine and tyrosine as amino acids are present in almost all dietary proteins. Normally, metabolic requirements for tyrosine are fulfilled from conversion of phenylalamine to tyrosine, as well as from tyrosine in the food. Tyrosine is metabolized to important compounds at three different sites in the body. In the thyroid gland it is iodinated, ultimately forming thyroxin. In the adrenal gland it is converted to epinephrine, and in melanocytes it is converted to melanin. Four diseases are associated with metabolic blocks at various points in the metabolism of phenylalamine and tyrosine, and three are associated with pigmentary changes in the skin and with phenyluria, albinuria and alkaptonuria. Epinephrine is probably not involved in human melanogenesis. In phenyluria there is a relative decrease in the melanin precursor, tyrosine. Recently, it was demonstrated that the skin in albinos contains as many melanocytes as normal skin. Tyrosinase has not been demonstrated in albino melanocytes, although recent copper studies on serum and hair showed the copper within normal limits. It seems likely, therefore, that albinism represents an inability to convert tyrosine to melanin. If human melanin formation occurred by any means besides enzymatic processes it would be expected to appear in albino tissue. Although much work remains to be done, the fundamental basis of the pigmenting process is evident.

"FATHER TO THE MAN"

HARVARD University recently announced a new co-operative effort to study the emotional difficulties of childhood and, on the assumption that the child is truly father to the man, to make a somewhat better parent of him. Allied in this attack on the behavioral problems of childhood, which will cover the whole period from infancy through adolescence, are the Harvard Medical School, the Boston Children's Hospital and the Judge Baker Guidance Center.

Psychiatry, under the new setup, will become a major service in the hospital, of equal rank with medicine and surgery; the new division will be part of the Harvard Department of Psychiatry. Dr. George E. Gardner, a recognized authority on child guidance, will be in charge of the new program as clinical professor of psychiatry at Harvard and psychiatrist-in-chief at the Children's Hospital.

Since the success of any enterprise is determined mainly by the capabilities of the persons who are concerned with it, the selection of Dr. Gardner

means that this constellation of agencies will be guided with intelligence, judgment and understanding. Director of the Judge Baker Center since 1941, Dr. Gardner has been clinical psychologist and senior psychiatrist at the McLean Hospital, research fellow in pediatrics at the Massachusetts General Hospital, and psychiatrist to the Juvenile Court of Boston. A graduate of Dartmouth College in 1925 he received his degree in medicine at Harvard in 1937, having meanwhile taken a master's degree in education in 1926 and a Ph.D. in 1930 in addition to his service as psychologist at McLean Hospital.

The new enterprise is in line with the accepted principle of having first things come first; the fact that there are six accredited agencies in Boston for training in child guidance shows that already much attention is being given to this field. Important among these agencies, which will undoubtedly contribute greatly to the success of the present cooperative program, is the James Jackson Putnam Children's Center, developed during the last decade under the able direction of Dr. Marian C. Putnam and Mrs. Beata Rank.

Human personalities, to use a worn simile, may be considered as composed of various types and mixtures of clay that cannot be altered but can be molded along certain patterns before they harden and dry. Too great enthusiasm about the influence of the environment, important as it is, should not blind one to the inescapable fact of structural differences and inequalities in the material, which must be worked before it sets. These differences, imposing their arbitrary limitations on the quality of the final product, are always recognized in any intelligent attack on the problems of behavior of any living organism.

No one can appreciate these individual restrictions better than Dr. Gardner, who sees in them not a cause for discouragement in approaching the problem with which he has worked so long, but a reason for tempering with discriminating judgment the concept of what can be accomplished. It is the wishful thinker who leaps from the first presentation of a problem to its complete and satisfactory solution, disregarding the slow steps that must be taken and the partial gains that must so often be accepted as the final reward.

There is more to the shaping of human destinies than the simple botanical exercise that Pope envisaged:

> 'Tis education forms the common mind;
> Just as the twig is bent the tree's inclined.

NOBEL PRIZE IN CHEMISTRY

THE 1953 award of the Nobel Prize in Chemistry (like that in literature to Her Majesty's first minister) comes not as a surprise but as an example of the appropriate and felicitous judgment that characterizes the choice of prize winners each year. Dr. Fritz Lipmann, professor of biologic chemistry at Harvard Medical School and chief of the Biochemical Research Laboratories at the Massachusetts General Hospital, shares the honor with Dr. Hans A. Krebs, of Sheffield University in England. This recognition of the outstanding service to mankind represented by Dr. Lipmann's work on the mechanisms of biosynthesis, leading to the discovery of coenzyme A, and on the mode of action of the thyroid hormone is welcomed with enthusiasm by those familiar with his accomplishments in these fields.

Born in Königsberg, Prussia, Dr. Lipmann received his training in medicine and chemistry at the University of Berlin, beginning his studies in biochemistry almost at the outset of his career. His investigations in Europe included research in Berlin and Copenhagen. In the United States he has worked not only at the Rockefeller Institute for Medical Research and Cornell University but also, since 1941, at the Massachusetts General Hospital and, since 1944, at Harvard Medical School. Previous expressions of approbation include honorary degrees of doctor of medicine from the University of Marseilles and doctor of science from the University of Chicago.

Through the award of the Nobel Prize his fellows acclaim the achievements of a man still in his vigorous prime. All who join in congratulations to Dr. Lipmann are confident of productive work of equal distinction in the future.

The New York Times states that the New York County Medical Society lately held a meeting in the Tombs.

Boston M. & S. J., *November 30, 1853*

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

COMMUNICABLE DISEASES IN MASSACHUSETTS FOR OCTOBER, 1953

RÉSUMÉ

Disease	October 1953	October 1952	Seven-Year Median
Chancroid	6	5	2
Chicken pox	264	394	394
Diphtheria	5	0	12
Dog bite	820	982	936
Dysentery, bacillary	73	27	15
Encephalitis, infectious	2	2	1
German measles	38	54	52
Gonorrhea	266	239	260
Granuloma inguinale	0	0	0
Hepatitis, infectious	93	76	31‡
Lymphogranuloma venereum	0	0	0
Malaria	6	12	4
Measles	23	76	126
Meningitis, meningococcal	8	6	6
Meningitis, Pfeiffer bacillus	5	0	2
Meningitis, pneumococcal	1	2	1
Meningitis, staphylococcal	0	0	0
Meningitis, streptococcal	0	0	0
Meningitis, undetermined	7	4	6
Mumps	446	260	275
Poliomyelitis	125	109	108
Salmonellosis	14	13	13
Scarlet fever	107*	134	151
Syphilis	182	191	191
Trichinosis	2	1	4
Tuberculosis, pulmonary	157	220	171
Tuberculosis, other forms	5	9	11
Typhoid fever	2	6	3
Undulant fever	1	1	3
Whooping cough	174	128	267

*Includes streptococcal sore throat.

‡Four-year median.

Comment

Diseases below the seven-year median were chicken pox, diphtheria, German measles, measles, scarlet fever and whooping cough.

Five cases of diphtheria were reported during October. Although the number was greater than that in the preceding month, only 26 cases have been reported since January 1.

The 38 cases of German measles reported during October made this the lowest figure for this month since 1944.

The 23 cases of measles and 109 cases of scarlet fever reported represented the lowest figures ever recorded for these diseases during the month of October in this state.

Diseases above the seven-year median were bacillary dysentery, infectious hepatitis and mumps.

The 73 cases of bacillary dysentery reported, although quite high for the month of October, represent a substantial drop from the number reported in the preceding three months of this year.

Geographical Distribution of Certain Diseases

The following diseases were reported from the communities named:

Diphtheria: Boston, 1; Brockton, 1; Everett, 1; Lawrence, 1; Lowell, 1; total, 5.

Dysentery, bacillary: Boston, 14; Brockton, 1; Cambridge, 12; Fitchburg, 2; Lawrence, 1; Lowell, 5; Malden, 2; Medford, 1; Melrose, 3; Methuen, 1; Milton, 3; Natick, 3; Newton, 6; Somerville, 2; Springfield, 1; Tewksbury, 1; Tewksbury State Hospital, 1; Watertown, 4; Wenham, 1; Worcester, 9; total, 73.

Encephalitis, infectious: Quincy, 1; Westfield, 1; total, 2.

Hepatitis, infectious: Athol, 1; Belchertown, 1; Boston, 35; Bourne, 1; Brookline, 2; Cambridge, 4; Chelsea, 2; Concord, 1; Framingham, 1; Haverhill, 1; Holden, 1; Leicester, 1; Malden, 1; Millbury, 1; Newton, 2; Oxford, 3; Paxton, 4; Pittsfield, 1; Richmond, 9; Shrewsbury, 1; Springfield, 3; Sutton, 3; Upton, 1; West Stockbridge, 1; Williamstown, 1; Worcester, 11; total, 93.

Lymphocytic choriomeningitis: Worcester, 1.

Malaria: Boston, 1; Fort Devens, 3; Salem, 1; Swansea, 1; total, 6.

Meningitis, meningococcal: Boston, 1; Brockton, 1; Fitchburg, 1; Fort Devens, 1; Medford, 1; Springfield, 2; Upton, 1; total, 8.

Meningitis, Pfeiffer bacillus: Andover, 1; Boston, 1; East Longmeadow, 1; North Adams, 1; Webster, 1; total, 5.

Meningitis, pneumococcal: Stockbridge, 1.

Meningitis, undetermined: Dalton, 1; Fall River, 1; Lowell, 1; Waltham, 1; West Boylston, 1; Worcester, 2; total, 7.

Poliomyelitis: Acushnet, 1; Arlington, 3; Attleboro, 1; Bedford, 5; Belchertown, 2; Bellingham, 1; Beverly, 2; Billerica, 1; Boston, 10; Brockton, 4; Cambridge, 1; Charlton, 1; Danvers, 1; Dartmouth, 1; East Bridgewater, 1; Easton, 2; Fall River, 2; Great Barrington, 1; Greenfield, 2; Haverhill, 13; Holyoke, 3; Hull, 1; Lexington, 1; Ludlow, 2; Malden, 2; Marlboro, 2; Marshfield, 2; Medfield, 1; Medford, 1; Melrose, 1; Middleboro, 1; Natick, 2; Needham, 1; New Bedford, 1; Newton, 7; Northampton, 2; Norwood, 3; Paxton, 1; Pittsfield, 2; Quincy, 1; Salem, 3; Saugus, 1; Shrewsbury, 1; Somerville, 3; South Hadley, 1; Springfield, 7; Templeton, 1; Topsfield, 1; Tyngsboro, 1; Wakefield, 1; Waltham, 2; Ware, 1; Wayland, 1; Wellesley, 1; West Springfield, 1; Weston, 1; Wilmington, 1; Winchendon, 1; Worcester, 4; total, 125.

Salmonellosis: Boston, 5; Brookline, 1; Cambridge, 2; Leominster, 2; Malden, 1; Newton, 1; Springfield, 2; total, 14.

Tetanus: Springfield, 1.

Trichinosis: Fall River, 1; Framingham, 1; total, 2.

Typhoid fever: Fall River, 1; Norwood, 1; total, 2.

Undulant fever: Marlboro, 1.

CORRESPONDENCE

MASSACHUSETTS ASSOCIATION OF MEDICAL TECHNOLOGISTS, INCORPORATED

To the Editor: Recently, physicians have been circularized by an organization calling itself the Massachusetts State Society of the American Medical Technologists announcing the start of a fund-raising campaign and requesting contributions from physicians to finance seminars and refresher courses for medical technologists. It should be clearly understood that the American Society of Medical Technologists, of which the Massachusetts Association of Medical Technologists is the local division, is *not* the group soliciting these funds. We are the organization recognized by the American Society of Clinical Pathologists. A qualified medical technologist may become a member of the American Society of Medical Technologists by meeting certain required educational standards and passing an examination given by the Board of Registry of the American Society of Clinical Pathologists. Such a technologist then has the privilege of using the designation M.T. (ASCP) after his name. This classification has been accepted by the American Medical Association, the American Hospital Association and the Catholic Hospital Association and signifies that the technologist has met the high requirements of this organization.

The Massachusetts Association of Medical Technologists has never found it necessary to appeal for funds to support seminars and refresher courses although it sponsors yearly state seminars and has an educational program in association with the annual meeting of the parent society. These are supported in part by the Board of Registry Seminar Fund and by the registration fees of those in attendance, as are most other medical organizations. Physicians have been very generous in responding to requests for their time to participate in these educational programs and have made the association a successful and rapidly growing organization.

Because of the confusion arising from the similarity in names and the fact that many physicians do not realize the "Massachusetts State Society of the American Medical Technologists" is not part of the nationwide organization recognized by clinical pathologists, we have considered it necessary to call this to your attention. We hope each district medical society will bring this matter to the attention of its members.

Helen J. Madden, M. T. (ASCP)
President
Boston Massachusetts Association of Medical Technologists

NONCLINICAL NOTES

ALVARENGA PRIZE

Dr. Francis D. Moore, Moseley Professor of Surgery, Harvard Medical School, and surgeon-in-chief, Peter Bent Brigham Hospital, has been awarded the Alvarenga Prize for 1953 for his work in metabolic changes after surgery.

NOTICES

ESSEX NORTH DISTRICT MEDICAL SOCIETY

The 113th winter meeting of the Essex North District Medical Society will be held at the Pentucket Club, 111 Main Street, Haverhill, on Wednesday afternoon, January 13, 1954. Dinner will be served promptly at 1:15 p.m.

The 113th annual meeting of the Essex North District Medical Society will be held at the Andover Country Club, Andover, on Wednesday evening, May 12, 1954. Dinner will be served promptly at 6:45 p.m.

NEW ENGLAND CENTER HOSPITAL HOUSE OFFICERS' ASSOCIATION

The House Officers' Association of the New England Center Hospital will present Dr. Rosalind Pitt-Rivers, of London, who will speak on the subject "Tri-iodothyronine and Thyroid Function," in the Stearns Auditorium, New England Center Hospital, on December 1, at 7 p.m. All interested persons are invited to attend.

INTERNATIONAL CANCER CONGRESS

The sixth International Cancer Congress, under the auspices of the International Union Against Cancer, will be held in Sao Paulo, Brazil, July 23 to 29, 1954. Physicians and scientists are invited to present papers of major current investigative work at this meeting. Registration blanks may be obtained from the Chairman, National Committee on the International Union Against Cancer, National Research Council, 2101 Constitution Avenue, Washington 25, D. C., who must also receive five copies of an abstract (not over 250 words) of each paper proposed for presentation accompanied by a letter of approval from the laboratory director or appropriate administrative officer before January 15, 1954. Information concerning travel arrangements may be obtained from Dr. Brewster S. Miller, American Cancer Society, Inc., 47 Beaver Street, New York 4, New York.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY

The next scheduled examination (Part I), written, and review of case histories, for all candidates will be held in various cities of the United States, Canada and military centers outside the continental United States on Friday, February 5, 1954.

Candidates resubmitting case abstracts should forward them as soon as possible to Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6, Ohio.

Requests for re-examination in Part II must be made by the candidate before February 1 of any year.

AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

The twelfth annual meeting of the American Academy of Dermatology and Syphilology will be held at the Palmer House, Chicago, December 5 to 10. The program will include lectures, panels, symposiums and discussions. Special lectures will be given by Drs. Walter Bauer, Thomas B. Fitzpatrick and A. Bunsen Lerner.

AMERICAN SOCIETY OF HUMAN GENETICS

The sixth annual meeting of the American Society of Human Genetics will be held at the Sheraton Plaza Hotel, Boston, December 28 through 30. There will be three symposiums: "Genetic Factors Affecting Intelligence," "Genetics and the Races of Man" and "Human Genetics and Medical Education." Further information may be obtained from Dr. Arthur G. Steinberg, Children's Medical Center, Boston.

SOCIETY MEETINGS AND CONFERENCES

DECEMBER 1. New England Center Hospital House Officers' Association. Notice above.

DECEMBER 2. Course in Child Psychiatry (Pediatric Neuropsychiatry). Page 428, issue of September 3.

DECEMBER 2. New England Conference on Allergy and Related Subjects. Page 828, issue of November 12.

DECEMBER 4 and 18. Boston Lying-in Hospital Journal Club. Page 672, issue of October 15.

DECEMBER 4, FEBRUARY 5 and APRIL 9. New England Society of Anesthesiologists. Notice above.

DECEMBER 5–10. American Academy of Dermatology and Syphilology. Notice above.

DECEMBER 6. American Academy of Dental Medicine. Page 170, issue of July 23.

DECEMBER 8. New York Society for Circulatory Diseases. Page 870, issue of November 19.

DECEMBER 8 and 15. Boston City Hospital House Officers' Association Lectures. Page 789, issue of November 5.

DECEMBER 11 and 12. New York and Brooklyn Regional Committee on Trauma, American College of Surgeons. Page 828, issue of November 12.

DECEMBER 11 and 12. University of Buffalo Scientific Symposiums. Page 870, issue of November 19.

DECEMBER 21. Hartford Medical Society Program. Page 260, issue of August 6.

DECEMBER 28. American Association for the Advancement of Science. Page 828, issue of November 12.

DECEMBER 28–30. American Society of Human Genetics. Notice above.

JANUARY 6, MARCH 3 and APRIL 21, 1954. Massachusetts Society for Research in Psychiatry. Page 750, issue of October 29.

JANUARY 22, 23, 29 and 30. International College of Surgeons Regional Meeting. Page 828, issue of November 12.

FEBRUARY 2–4. Examination for Public Health Service Medical Officers. Page 750, issue of October 29.

FEBRUARY 15–20. Pan-American Academy of General Practice. Page 750, issue of November 5.

MAY 31–JUNE 3. American Urological Association. Page xvii, issue of July 23.

JULY 22 and 23. International College of Surgeons. Regional Meeting. Page 828, issue of November 12.

JULY 23–29. International Cancer Congress. Notice above.

SEPTEMBER 7–10. Nineteenth Annual Congress of the United States and Canadian Sections of the International College of Surgeons. Page 828, issue of November 12.

SEPTEMBER 12–15. Second International Congress of Cardiology. Page 44, issue of July 2.

SEPTEMBER 16–18. American Heart Association Annual Scientific Sessions. Page 44, issue of July 2.

DISTRICT MEDICAL SOCIETIES

ESSEX NORTH

JANUARY 13. Pentucket Club, 111 Main Street, Haverhill.
MAY 12. 113th Annual Meeting. Andover Country Club, Andover.

MIDDLESEX EAST

JANUARY 20. (Combined with the Auxiliary.)
MARCH 24.
MAY 11. Annual Meeting. (Harlow Dinner.)

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 3

THURSDAY, DECEMBER 3

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Cardiac Grand Rounds. Main Amphitheater, Children's Medical Center.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*4:00–5:00 p.m. Metabolic Requirements of Nutrition in Normal and Abnormal States. Dr. H. Minkel. Nurses' Home, Cambridge City Hospital.
*5:00–6:00 p.m. Surgical Division Meeting. Mount Auburn Hospital, Cambridge.
8:15 p.m. Deaconess Medical Lecture. Ventricular Hypertrophies. Dr. F. E. Hinton. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, DECEMBER 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Tumors of Head and Neck. Dr. F. Cahill. Ward B Classroom, Cambridge City Hospital.

(Notices concluded on page xv)

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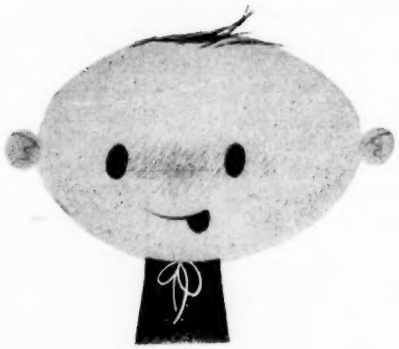

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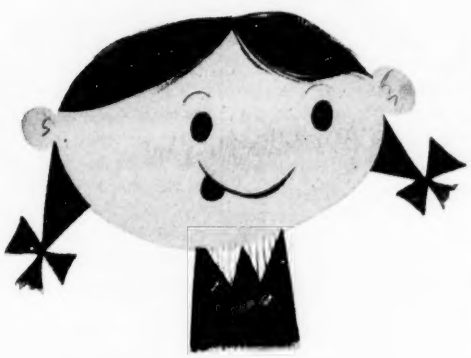

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1. Howard, J. E. Protein Metabolism During Convalescence After Trauma. Arch. Surg. 50:166, 1945.
2. Co Tui. Minutes of the Conference on Metabolism Aspects of Convalescence Including Bone and Wound Healing. Josiah Macy, Jr. Foundation, Fifth Meeting Oct. 8-9, p. 57, 1943.
3. Whipple, G. H. and Madden, S. C. Hemoglobin, Plasma Protein and Cell Protein: Their Interchange and Construction in Emergencies. Medicine 23:215, 1944.
4. Mulholland, J. H., Co Tui, Wright, A. M., Vinci, V., and Shafiroff, B. Protein Metabolism and Bed Sores. Am. Surg. 118:1015, 1943.

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NOTICES *(Concluded from page 914)*

*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.

*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.

*3:00–4:00 p.m. X-ray Conference. Dr. F. Herzan. Ward B Classroom, Cambridge City Hospital.

*4:00–5:00 p.m. Journal Club Meeting. Significance of Urinary Infection in Pregnancy and the Postpartum Period. Dr. J. Hartwell Harrison. Boston Lying-in Hospital Auditorium, 221 Longwood Avenue.

*4:00–10.00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Waltham Street.

SATURDAY, DECEMBER 5

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00 a.m. Proctology Clinic. Peter Bent Brigham Hospital.

*9:00 a.m. Alcoholism Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

11:00 a.m.–12:00 m. Blood Clinic. Dr. William Dameshek. Stearns Auditorium, New England Center Hospital.

MONDAY, DECEMBER 7

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Foot Problems. New England Deaconess Hospital.

8:30–9:30 a.m. Clinic by entire Surgical Staff and Anesthesia Staff. Cheever Amphitheater, Dowling Building, Boston City Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

12:00 m. Clinicopathological Conference (Boston Floating Hospital). Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.

7:00–9:00 p.m. Combined Anesthesia Residents' Training Program. Jimmy Fund Auditorium, Children's Medical Center, 35 Binney Street.

TUESDAY, DECEMBER 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Pediatric Grand Rounds. Cheever Amphitheater, Dowling Building, Boston City Hospital.

*12:00 m.–1:00 p.m. Pediatric Rounds. Burnham Memorial Hospital for Children, Massachusetts General Hospital.

*12:15–1:15 p.m. X-ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.

*12:30–1 30 p.m. Medical Journal Club. Cafeteria. New England Deaconess Hospital.

*4:30–5:30 p.m. Anesthesia Teaching Conference. Stearns Auditorium, New England Center Hospital.

*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.

*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical), Faulkner Hospital.

7:00 p.m. Boston City Hospital House Officers' Association. Apical Localization of Pulmonary Tuberculosis. Dr. William Dock. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, DECEMBER 9

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

*12:00 m. Boston State Hospital Psychiatric Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.

*12:00 m.–1:00 p.m. Clinicopathological Conference (Children's Medical Center). Jimmy Fund Building, 35 Binney Street.

*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.

12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.

*1:30–2:30 p.m. Pathological Conference. Dr. C. Jones. Nurses' Home, Cambridge City Hospital.

2:00–3:00 p.m. Pediatric Conference for Practitioners (Children's Medical Center). Jimmy Fund Building, 35 Binney Street.

*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.

*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.

*5:00–6:00 p.m. American Cancer Society Telecast. Modern Approach to Abdominal Cancer. Drs. Milton Porter and Charles Flood. Children's Cancer Research Center, 35 Binney Street.

7:30–9:30 p.m. Lahey Clinic Lecture. Mechanism of Action of Anti-thyroid Drugs. Pathology of the Thyroid Gland. Drs. Elmer Bartels and William Meissner. Joslin Auditorium, New England Deaconess Hospital.

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1. Frost, L. H., and Jackson, R. L.: J. Pediat. 39: 585-592, 1951.

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